Chronic Pancreatitis

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Chronic Pancreatitis

- Definition
  - A pathologic fibro-inflammatory syndrome of the pancreas in individuals with genetic, environmental and/or other risk factors who develop persistent pathologic responses to parenchymal injury or stress
- Characteristics
  - Pancreatic atrophy, fibrosis, pain syndromes, duct distortion and strictures, calcifications, pancreatic exocrine dysfunction, pancreatic endocrine dysfunction and dysplasia

Whitcomb DC et al. *Front. Pediatr.* 2022. 10:941852
Whitcomb et al. Pancreatology. 2016 ; 16(2): 218–224

Risk Factors/Etiologies

- TIGAR-O V2

T : Toxin- Metabolic	Alcohol, Smoking, Hypercalcemia, Hypertriglyceridemia
I : Idiopathic	Early onset(<35yr), Late onset(>35 yr)
G : Genetic	Autosomal dominant(PRSS1), Autosomal recessive(CFTR,SPINK1)
A : Autoimmune	Autoimmune type 1- IgG4 related, Autoimmune type 2
R : RAP & SAP	Severe acute pancreatitis – Recurrent acute pancreatitis
O : Obstructive	Pancreas divisum, Ampullary stenosis, Main duct pancreatic stone, Mass causing duct obstruction

Whitcomb DC et al. Clinical and Translational Gastroenterology 2019;10:e-00027

Table 2. The M-ANNHEIM multiple risk factor classification of chronic pancreatitis

	M Pancreatitis with Multiple risk factors
A	**A**lcohol consumption
	Excessive consumption (>80 g/day)
	Increased consumption (20–80 g/day)
	Moderate consumption (<20 g/day)
N	**N**icotine consumption
	(In cigarette smokers: description of nicotine consumption by pack-years)
N	**N**utritional factors
	Nutrition (e.g., high caloric proportion of fat and protein)
	Hyperlipidemia
H	**H**ereditary factors[a]
	Hereditary pancreatitis (defined according to Whitcomb[96])
	Familial pancreatitis (defined according to Whitcomb[96])
	Early-onset idiopathic pancreatitis
	Late-onset idiopathic pancreatitis
	Tropical pancreatitis
	(possible mutations in the *PRSS1*, *CFTR*, or *SPINK1* genes)
E	**E**fferent duct factors
	Pancreas divisum
	Annular pancreas and other congenital abnormalities of the pancreas
	Pancreatic duct obstruction (e.g., tumors)
	Posttraumatic pancreatic duct scars
	Sphincter of Oddi dysfunction
I	**I**mmunological Factors
	Autoimmune pancreatitis
	Sjögren syndrome-associated chronic pancreatitis
	Inflammatory bowel disease-associated chronic pancreatitis
	Chronic pancreatitis with autoimmune diseases
	(e.g., primary sclerosing cholangitis, primary biliary cirrhosis)
M	**M**iscellaneous and rare metabolic factors
	Hypercalcemia and hyperparathyroidism
	Chronic renal failure
	Drugs
	Toxins

The M-ANNHEIM classification is based on the assumption that, in the majority of patients, chronic pancreatitis results from the interaction of multiple risk factors (M). The different risk factors are grouped into the major subcategories of alcohol consumption (A), nicotine consumption (N), nutritional factors (N), hereditary factors (H), efferent pancreatic duct factors (E), immunological factors (I), and various rare miscellaneous and metabolic factors (M)

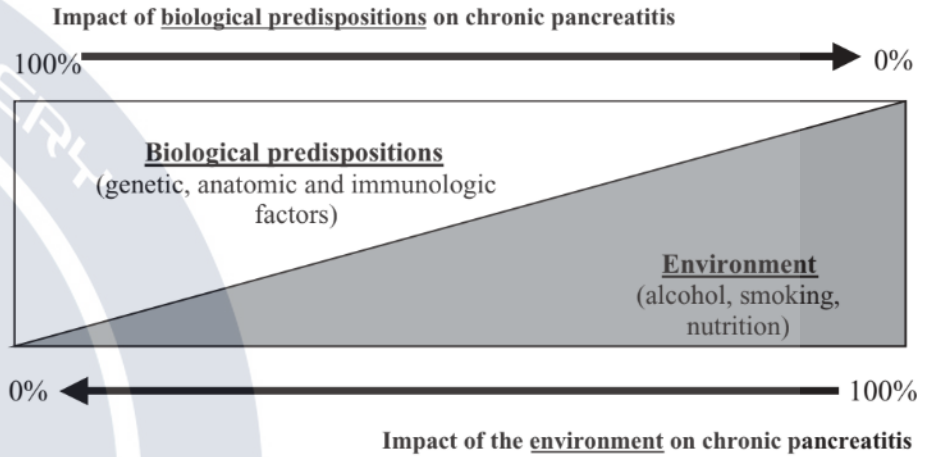

Fig. 1. Interaction of biological predispositions with the environment in chronic pancreatitis. The M-ANNHEIM classification is based on the assumption that chronic pancreatitis results from the interaction of multiple risk factors in the majority of patients. This interaction may be summarized as a continuum of various biological factors and environmental factors. Currently, an exact grading of the impact of each of these various risk factors on the development of the disease does not appear possible, as sufficient clinical and epidemiological data are not available. The M-ANNHEIM classification aims to provide a clinical tool to reveal the as yet unknown interactions of these risk factors with the development and course of chronic pancreatitis

A. Schneider et al.J Gastroenterol 2007; 42:101–119

Pathogenesis

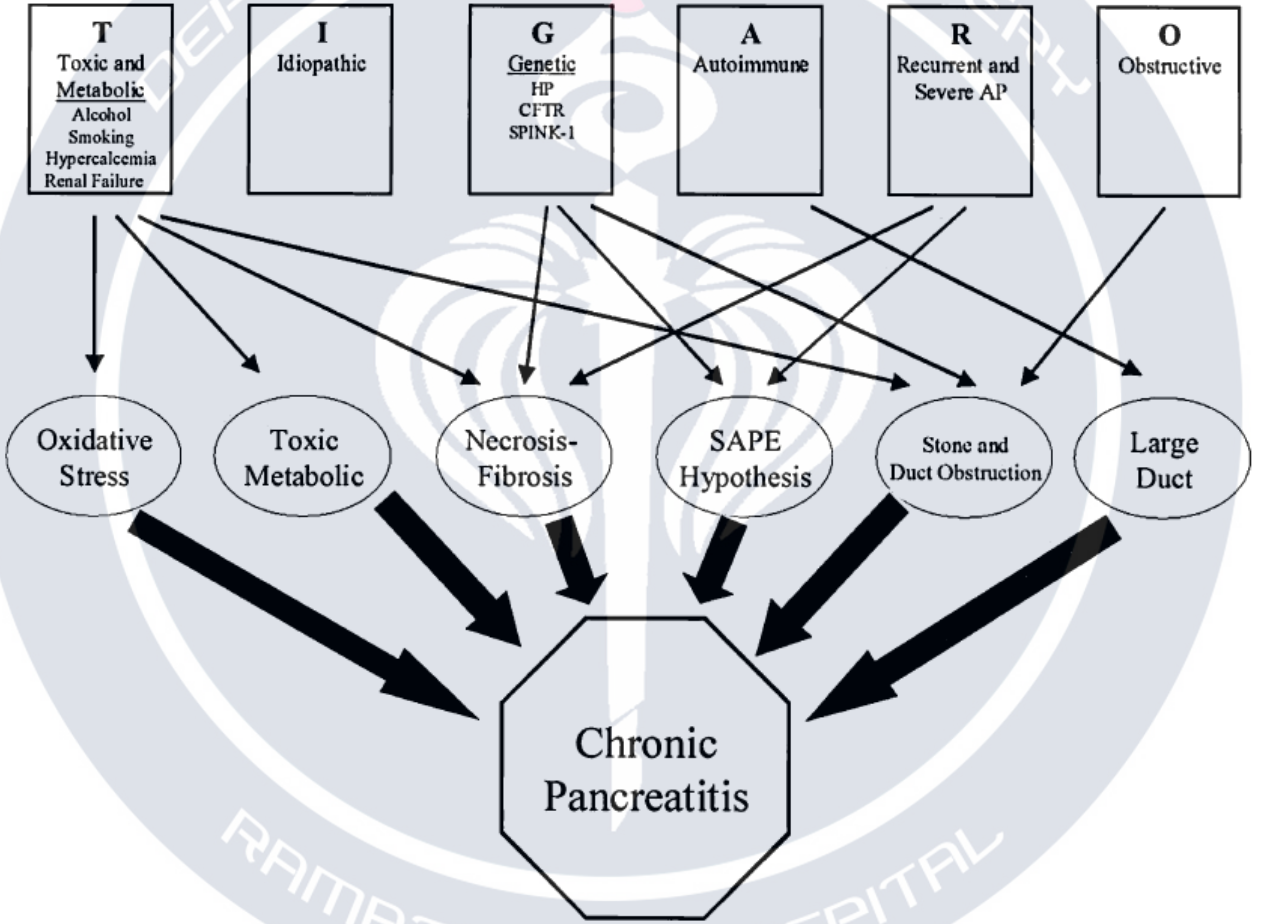

Figure 6. Pathogenic pathways proposed to explain each etiology of CP enumerated in the TIGAR-O classification. It is likely that different pathophysiologic mechanisms may explain the diverse etiologies of CP.

T. Stevens et al.Am J Gastroenterol 2004 ; 99:2256-2270

Pathogenesis

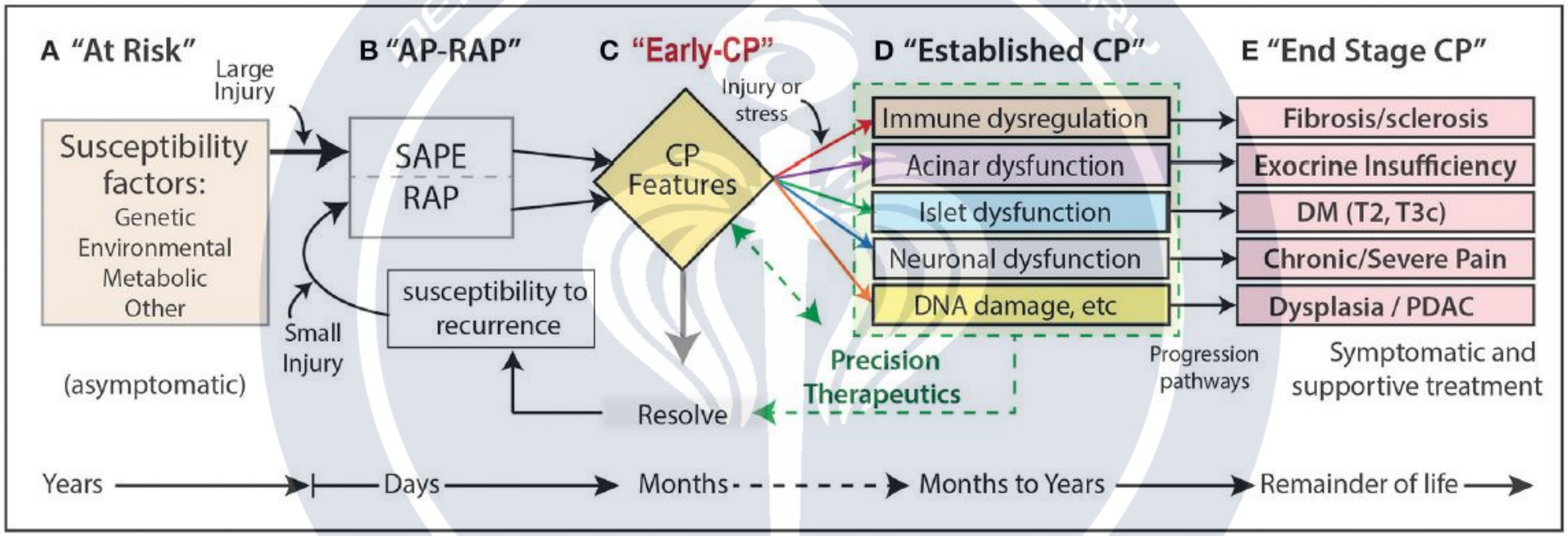

FIGURE 1
(A–E) Progressive CP pathogenesis. Five progressive stages can be defined that persist for days to many years. Each stage may have unique risk factors or stress/injury mechanisms, as well as innate compensatory or protective mechanisms that may be altered or defective in patients who progress. Stage B is a critical driver of the CP pathways as the initial episode of AP (SAPE) lowers the threshold for RAP. CP, chronic pancreatitis; DM, diabetes mellitus; RAP, recurrent acute pancreatitis; SAPE, sentinel acute pancreatitis event; PDAC, pancreatic ductal adenocarcinoma; T2, type II DM; T3c, type IIIc diabetes caused by exocrine pancreas pathology or surgery.

Whitcomb DC (2022) Central role of the sentinel acute pancreatitis event (SAPE) model in understanding recurrent acute pancreatitis (RAP): Implications for precision medicine. *Front. Pediatr. .2022.* 10:941852

Clinical Manifestation

- Abdominal pain
  - Most common symptomatic complaint : up to 80% of patients
  - Epigastric with radiation to the back
  - Initially intermittent and recurrent then persistent in later stage
    - Burn-out : Final stage of CP, complete absence of pain
- Exocrine insufficiency
  - Abdominal bloating or discomfort
  - Overt steatorrhea to weight loss in severe EPI
- Endocrine insufficiency : Chronic pancreatitis related DM – DM type 3c
- Pancreatic head mass/ cancer
- Course of chronic pancreatitis
  - Initial period w/o pain -> Abdominal pain -> Exocrine insufficiency with maldigestion -> Endocrine insufficiency

Hart and Conwell. Am J Gastroenterol. 2020 January; 115(1): 49–55

K. Bachmannetal.Best Practice & Research Clinical Gastroenterology.24(2010)299-310

Pathophysiology of Pain

- Abdominal pain : Most frequent symptom of CP about 85%
  - Severity, temporal nature, and natural history of pain is highly variable
  - Dull, sharp or nagging sensation in the upper abdomen, which can radiate to the back, and often presents after or worsened by food intake
- Pain in CP remains poorly understood and inadequately correlated with neurobiological mechanisms
- Changes in structure and function in both the peripheral and central nervous system
  - Maladaptive state that includes both neuropathic and dysfunctional pain

A.M. Drewes et al. Pancreatology 17 (2017) 720-731

Pathophysiology of Pain

- Pain classification
  - A-type pain “intermittent”
    - One or more discrete episodes of pain interspersed with pain-free intervals
  - B-type pain “constant”
    - Persistent (i.e. daily) pain over prolonged periods of time and/or closely clustered exacerbations of severe pain
- Burn-out hypothesis
  - Relation between pain relief and a longer disease duration with loss of pancreatic function in chronic pancreatitis
  - Severe pain is provoked by inflammation and that spontaneously pain relief will occur after long-standing disease with extensive fibrosis
  - Scientific evidence still doubtful

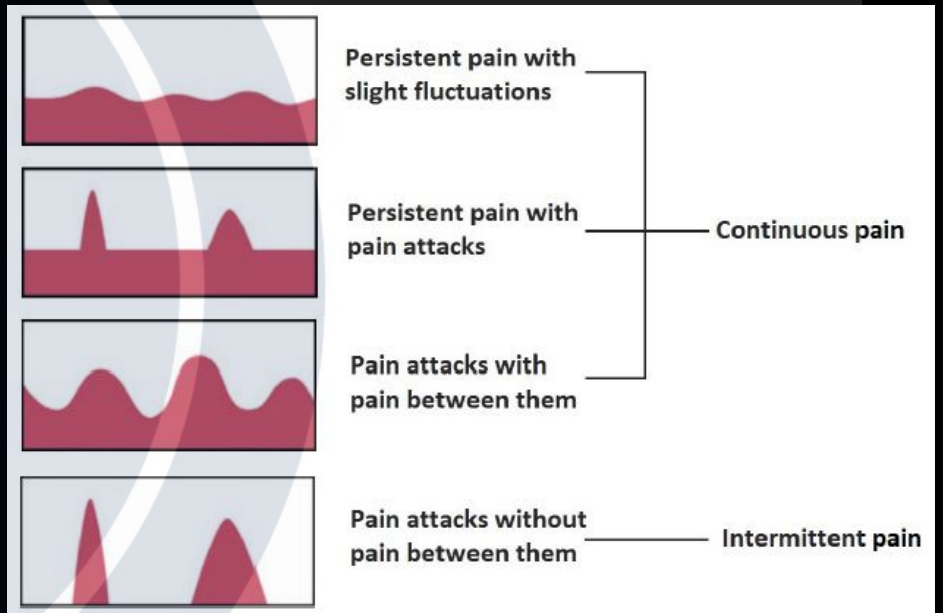

Figure 1 Pain pattern pictures. Pictures adapted from the PainDETECT Questionnaire.[16]

A.M. Drewes et al. Pancreatology 17 (2017) 720-731

Kempeneers MA, et al. Gut 2021;**70**:1724–1733. doi:10.1136/gutjnl-2020-322117

Pathophysiology of Pain

- Pain in chronic pancreatitis has a very unpredictable course
- Patients alternated between pain patterns regardless of any endoscopic or surgical intervention
- Changes in pain patterns seem to be represented by alternating periods of continuous pain that is severe and periods of intermittent pain which patients experience as less severe
- No morphological difference between pain pattern
  - Intraductal calcifications, pseudocysts, ductal dilatation
- Changes from pain to no-pain is very heterogeneous and not associated with disease duration nor exocrine/endocrine insufficiency
  - Refute burn-out theory

Kempeneers MA, et al. Gut 2021;**70**:1724–1733. doi:10.1136/gutjnl-2020-322117

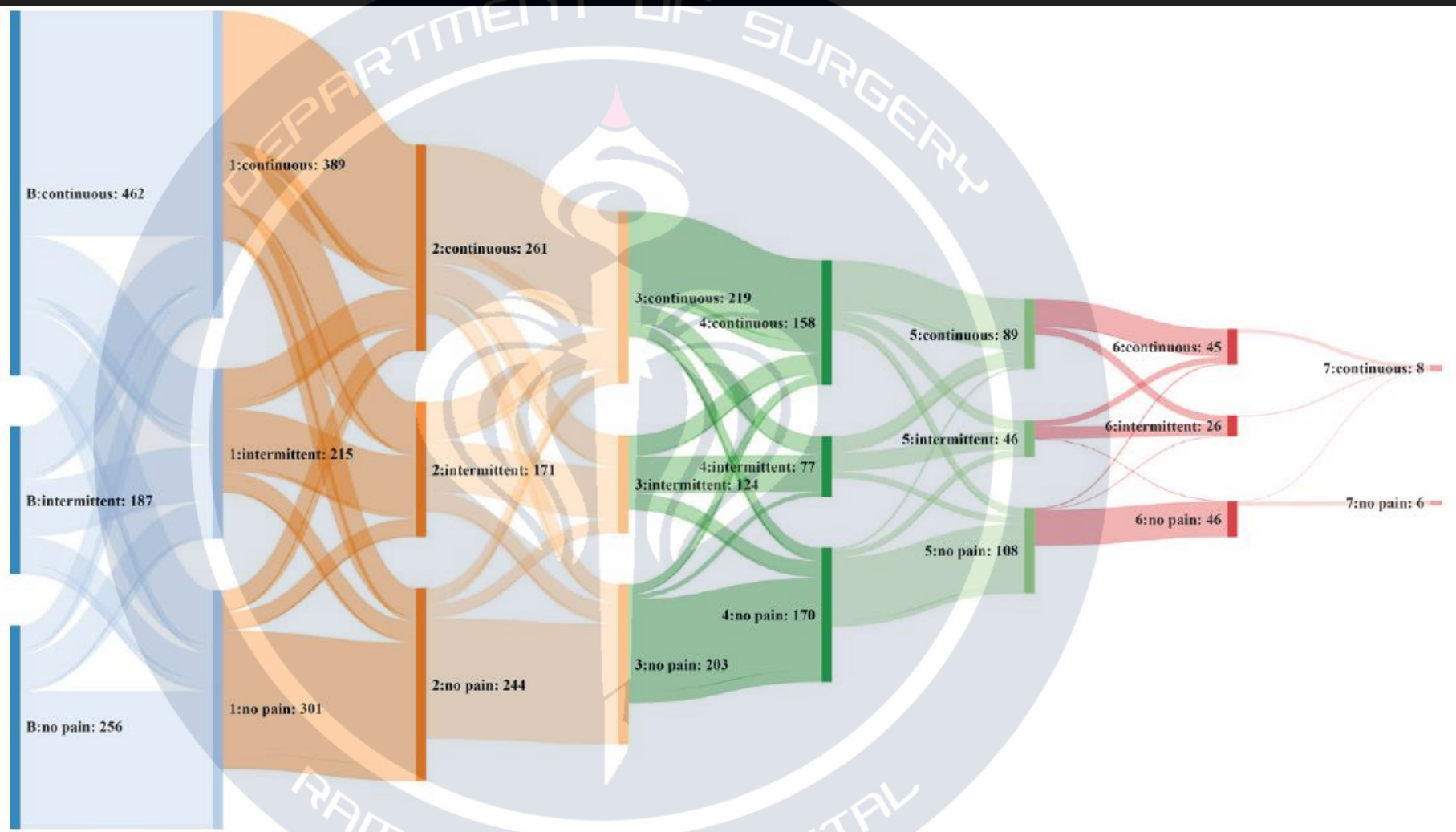

Figure 3 Sankey diagram of pain patterns during follow-up. Sixty-one per cent of patients had at least one pain pattern alteration.

Kempeneers MA, et al. Gut 2021;**70**:1724–1733. doi:10.1136/gutjnl-2020-322117

Pathophysiology of Pain

- Variety of potential pain mechanisms
  - Plumbing theory
    - Pain is generated by increased pressure in the pancreatic duct or in the pancreatic parenchyma
    - Most widely accepted theory regarding the cause of pain and it is the theoretical background of most interventions including surgical and endoscopic drainage procedures
      - Pancreatic duct hypertension
      - Pancreatic parenchymal hypertension
      - Pancreas morphology

Poulsen JL et al . Pain mechanisms in chronic pancreatitis.*World J Gastroenterol* 2013 November 14; 19(42): 7282-7291

Pathophysiology of Pain

- Variety of potential pain mechanisms
  - Wiring theory
    - Pain caused by a lesion or disease of the somatosensory system
    - Emerging histological and neurophysiological evidence of such lesions to peripheral nerves in the pancreatic gland and coincident aberrant central pain processing
      - Peripheral nociception, peripheral sensitization
        - Upregulation signaling molecules involved in inflammation and pronociceptive mediators, but also neurotrophic factors in CP
      - Pancreatic neuropathy
        - Increased neural density and hypertrophy, sprouting and neuritis of the intrapancreatic nerves, as well as activation of glia and immune cells -> remodeling of intrapancreatic innervation
      - Central mechanisms of pain, central sensitization
        - Increased synaptic efficiency established in sensory neurons in the dorsal horn of the spinal cord (and/or at supraspinal sites), following intense peripheral noxious stimuli, tissue injury, or nerve damage
        - Pain, which is no longer coupled to the presence, intensity, or duration of noxious peripheral stimuli

Poulsen JL et al . Pain mechanisms in chronic pancreatitis.*World J Gastroenterol* 2013 November 14; 19(42): 7282-7291

Pathophysiology of Pain

- Variety of potential pain mechanisms
  - Pancreatic and extrapancreatic complications
    - Pseudocysts
    - Biliary and duodenal obstruction
    - Peptic ulcer
  - Adverse effects to treatment
    - Opioids : GI adverse effects -> opioid-induced bowel dysfunction
    - Adverse effects of endoscopic or surgical treatment : ductal and parenchymal trauma, adhesion, pancreatic and bile duct strictures

Poulsen JL et al . Pain mechanisms in chronic pancreatitis.*World J Gastroenterol* 2013 November 14; 19(42): 7282-7291

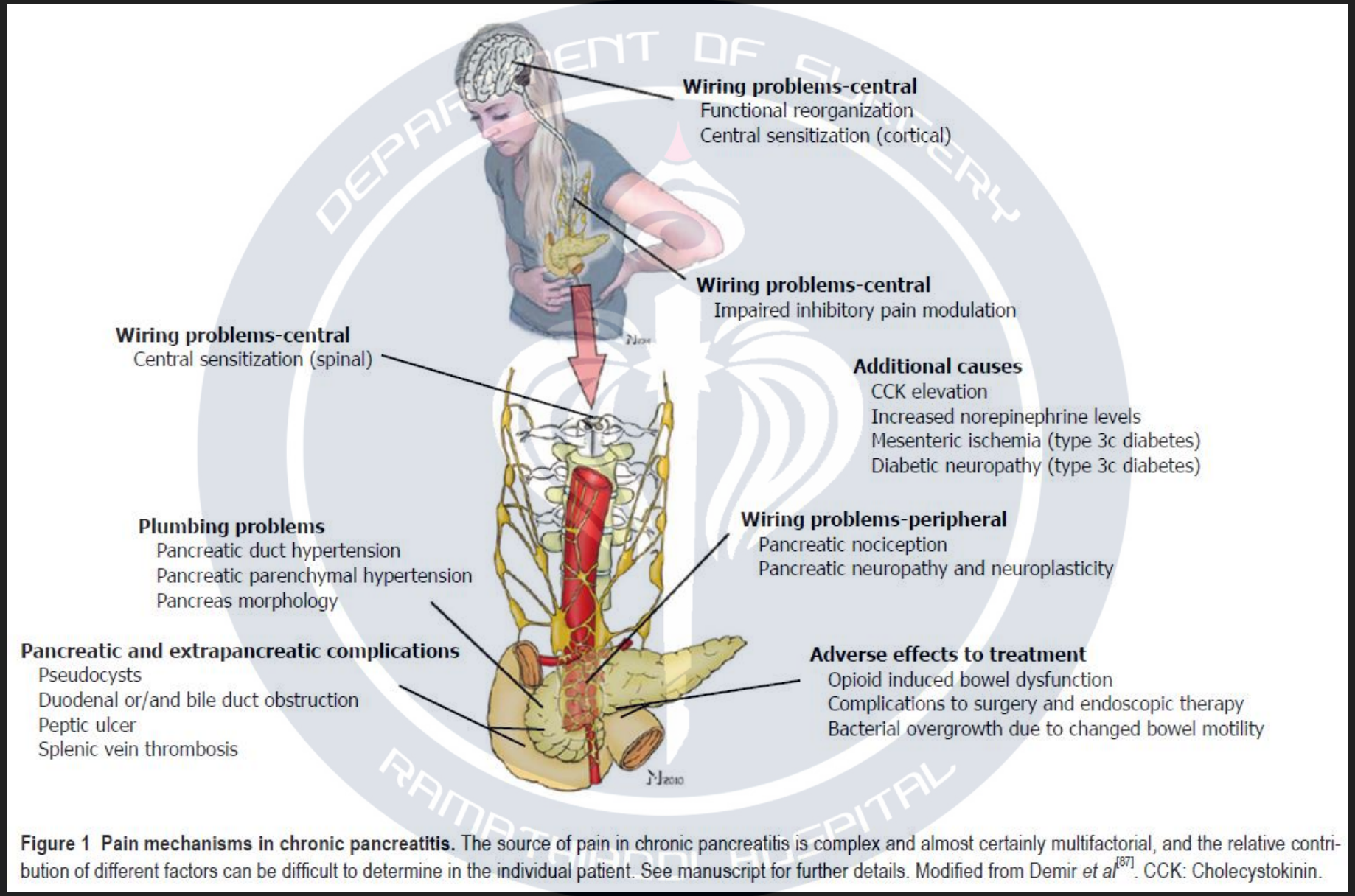

Figure 1 Pain mechanisms in chronic pancreatitis. The source of pain in chronic pancreatitis is complex and almost certainly multifactorial, and the relative contribution of different factors can be difficult to determine in the individual patient. See manuscript for further details. Modified from Demir *et al*[87]. CCK: Cholecystokinin.

Poulsen JL et al . Pain mechanisms in chronic pancreatitis.*World J Gastroenterol* 2013 November 14; 19(42): 7282-7291

Investigation

- Transabdominal ultrasound
  - Inexpensive, noninvasive, and readily available imaging tool
  - Useful in detecting gallstones and investigating biliary origins of pain for DDx
  - Poor visualization of the pancreas, mainly because of overlying gas-filled bowel loops, obesity, and technical and operator dependent factors
  - Sensitivity of ultrasound to detect chronic pancreatitis is as low as 48%
    - In advanced stage : Sensitivity increase to 96%, Specificity 75% - 90%
    - Detection of calcification and pseudocysts

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Investigation

- Diagnostic criteria for chronic pancreatitis by transabdominal ultrasound
  - Irregular contour (lobulation)
  - Pancreatic duct dilation and irregularity of the main pancreatic duct
  - Loss or reduction of pancreatic parenchyma echogenicity (echo-poor or echo-rich areas)
  - Cysts or cavities
  - Pancreatic calcifications

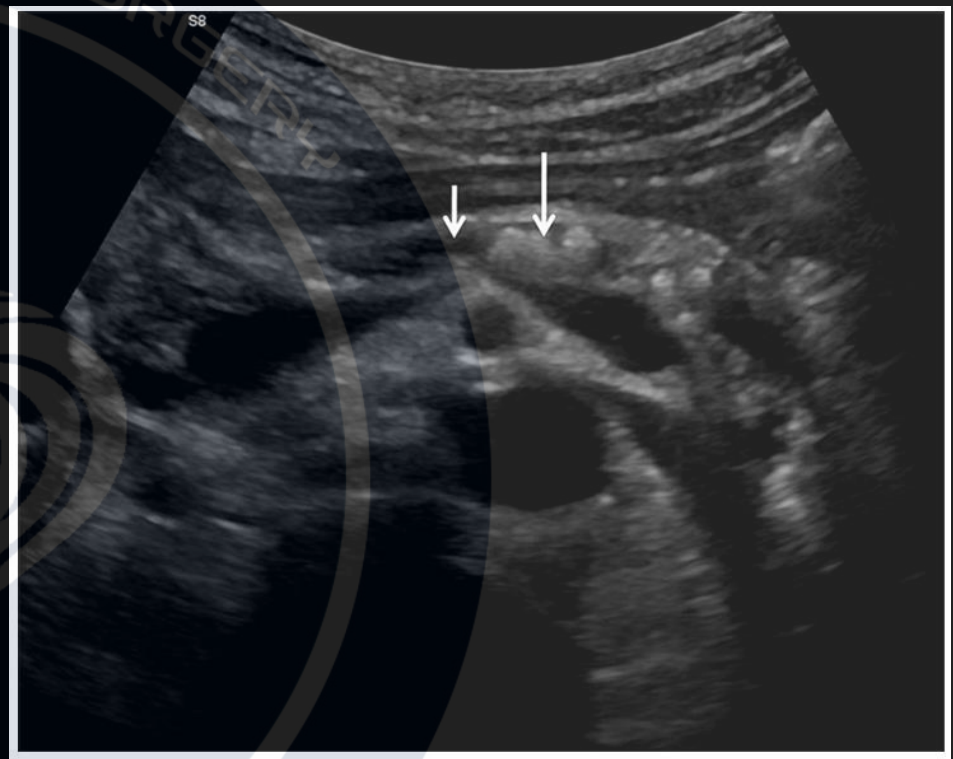

Figure 2: Abdominal ultrasound shows atrophic pancreas with dilated main pancreatic duct (short arrow) with intraductal calculi (arrow)

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Investigation

- Computed tomography
  - Findings : main pancreatic duct and secondary duct dilation, intraductal calcifications, gland atrophy, and cystic lesions
  - Most sensitive method to detect calculi in non-contrast phase
    - CT with contrast still allows for adequate detection of parenchymal calcifications
  - Difficult to differentiate from pancreatic cancer
    - Chronic pancreatitis are intraductal or parenchymal calcifications, lack of obstructing mass, irregular dilation of the pancreatic duct, and relatively limited atrophy of the gland
    - Findings favor neoplasia : Pancreatic duct dilation with associated mass at the site of obstruction, with associated atrophy of the pancreas, vascular invasion, and metastases
  - Sensitivity of 56% - 95%, Specificity of 85% - 100%
  - Useful to evaluate the extrapancreatic and peripancreatic organs and tissues
    - Can exclude complications of chronic pancreatitis such as pseudoaneurysms, pseudocysts, and thrombosis of the portosplenic circulation

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Investigation

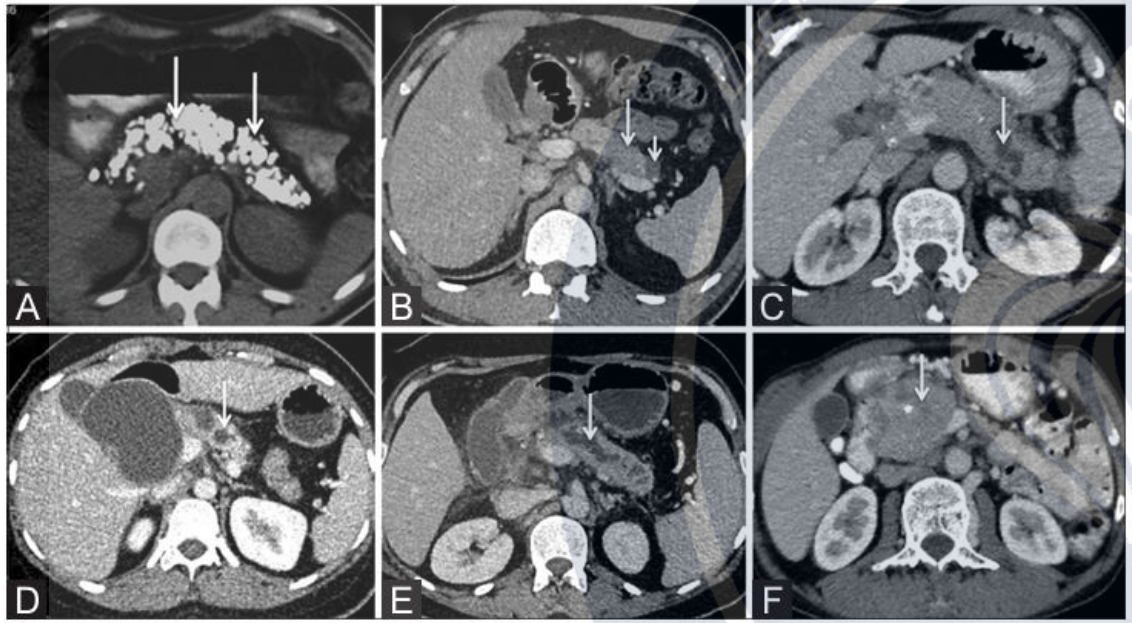

Figure 6 (A-F): CT findings in chronic pancreatitis: Non-contrast CT (A) shows extensive pancreatic calcifications (arrows). CT scan in another patient (B) shows pancreatic atrophy (arrow) and a small cystic area (short arrow). Pancreatic duct irregularity and varying degrees of dilatation is shown in C to E (arrow). A large pseudocyst is also seen in d. An intraductal calculus (arrow) with pancreatic head mass is seen in another patient (F)

Table 3: CT Features of CP

Common findings	% of cases
Ductal dilatation	68%
Parenchymal atrophy	54%
Parenchymal/ductal calcifications most specific feature[2] [Figure 4]	50%
Collections	30%
Glandular enlargement due to interlobular and periductal fibrosis[17,35]	30%
Bile duct dilatation	29%
Peripancreatic fat stranding	16%
Less common findings	
Heterogenous glandular enhancement (Delayed enhancement of the fibrosed parenchyma)[35]	
Diagnosis of obstructive causes of CP such as pancreatic ductal carcinomas, cystic tumours and rarely neuro-endocrine tumours which may lead to recurrent episodes of pancreatitis.	
Complications of CP:[35,36]	
Pseudoaneurysms	
Biliary obstruction	
Venous thrombosis	
Rare complications such as pancreatic-pleural and peritoneal fistulae can also be suspected on CT due to presence of pleural fluid and ascites respectively, however MRI/MRCP is superior in identifying these fistulae[37]	

Kamat, et al.: Imaging in chronic pancreatitis. Indian Journal of Radiology and Imaging / Volume 29 / Issue 2 / April-June 2019

Investigation

- Magnetic Resonance Imaging and Cholangiopancreatography
  - Recommend in patients without specific pathologic changes are seen on CT, but where the clinical suspicion of a diagnosis remains high
  - Useful in detecting early parenchymal and ductal changes that are typically missed by CT and ultrasound
  - Secretin-stimulated MRI/MRCP
    - Dynamic test to characterize the pancreatic duct and pancreatic parenchyma, and can more accurately detect subtle duct changes
    - Useful in patients in which the clinical suspicion is high, but standard MRI/MRCP was not diagnostic
    - Can also evaluate the exocrine function of the pancreas by estimate the fluid secreted by the pancreas after stimulation
  - Useful to evaluate for periductal fibrosis, ductal dilation with ectasia and side-branch abnormalities, intraparenchymal cyst formation, and pancreatic duct strictures and stones leading to obstructed outflow

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Table 4: MRI/MRCP Features of CP

MRI protocol: T1-w FSE, T2-w FSE, Pre/Post gadolinium GRE, MRCP[17]	
T1: Hypointense areas corresponding to the inflammation/fibrosis/focal lesion[44-46] [Figure 7B]	
Contrast enhanced T1: Heterogenous signals and delayed post-gadolinium enhancement due to presence of fibrotic areas which impede the capillary flow[8,47-49]	
Reduced antero-posterior thickness of the pancreas [Figure 8]	
Calcifications and ductal calculi show signal drop (Calcifications and air specks are better appreciated on CT)	
MRCP: Most useful for ductal assessment [Figure 9A to C]	
S-MRCP: Assessment of pancreatic secretory functions	
Modified MRCP Cambridge criteria for CP[51]:	
Cambridge 1 (normal)	Normal pancreas
Cambridge 2 (equivocal)	Dilatation/obstruction of <3 side branches with a normal MPD
Cambridge 3 (mild)	Dilatation/obstruction of >3 side branches with a normal MPD
Cambridge 4 (moderate)	Cambridge 3 with stenosis/dilatation of MPD
Cambridge 5 (severe)	Cambridge 3 and 4 plus additional obstructions, cysts, stenosis of the main pancreatic duct, and calculi.

FSE-Fast Spin Echo; GRE-Gradient Recalled Echo

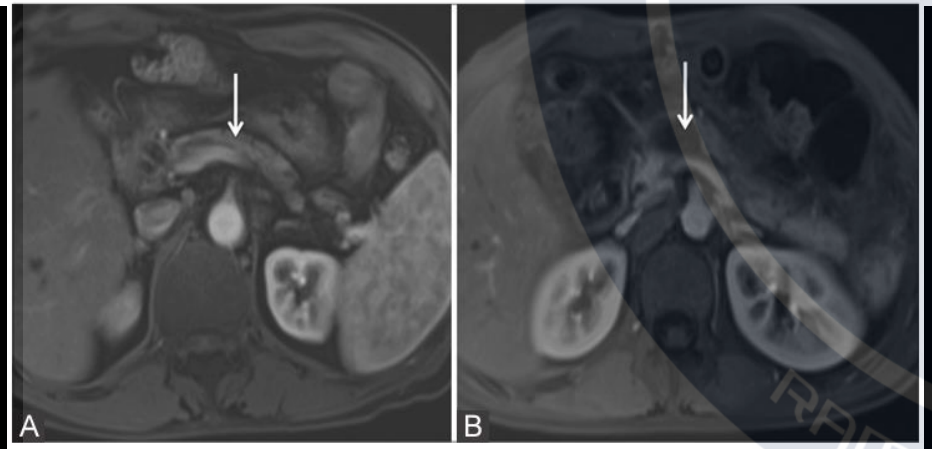

Figure 8 (A and B): MRI findings in chronic pancreatitis: Axial T1-weighted contrast enhanced MRI (A) shows reduced T1-weighted signal of the pancreas (arrow). Axial T1-weighted contrast enhanced MRI in another patient (B) shows mild reduction in bulk with a cystic lesion in neck of pancreas (arrow)

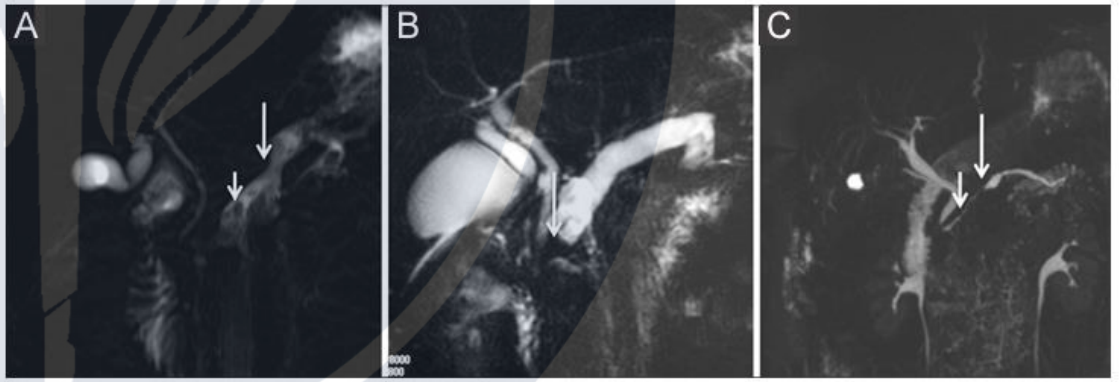

Figure 9 (A-C): MRCP findings in chronic pancreatitis: Multiple strictures (arrow) as well as filling defects (short arrow) within the main pancreatic duct are seen in A. In another patient (B), a large intraductal calculus (arrow) is causing marked dilatation of the pancreatic duct. MRCP in a different patient (C) shows strictures (arrow) and irregularity (short arrow) of the pancreatic duct

Investigation

- Endoscopic Retrograde Pancreatography
  - Previously held as gold standard, sensitivity 90% specificity nearly 100%
  - Invasive methods, low but important rate of Post-ERP Pancreatitis 3-10%
    - Currently mainly used as therapeutic tool
  - ERP staging system for the diagnosis of chronic pancreatitis -> based on pancreatic ductal changes
    - International definitions are based on ERP findings published in 1984 as the Cambridge criteria
  - Changes of early chronic pancreatitis may not be seen on ERP, which may assess ductal changes that occur in advanced disease, such as irregularity, dilation, tortuosity, stenosis, cysts, calculi, and bile duct stenosis

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Investigation

- Endoscopic Retrograde Pancreatography

Cambridge Criteria

Grade	Main Pancreatic Duct	Branch Ducts
Normal	Normal	Normal
Cambridge 1 (*equivocal*)	Normal	<3 abnormal
Cambridge 2 (*mild*)	Normal	3 abnormal
Cambridge 3 (*moderate*)	Abnormal	>3 abnormal
Cambridge 4 (*severe*)	Abnormal *	>3 abnormal

* Including large cavity >10 mm, Intraductal filling defects, duct obstruction (stricture), duct dilation or irregularity, calculi/pancreatic calcification, or contiguous organ invasion

A Anaizi, et al. Dig Dis Sci. 2017 July ; 62(7): 1713–1720. doi:10.1007/s10620-017-4493-2

Investigation

- Endoscopic ultrasonography
  - Most appropriate and sensitive imaging to diagnose intraductal and parenchymal changes, mainly during the early stage of disease
  - Indicated in patients with negative CT or MRI with clinical suspicion of chronic pancreatitis
  - High sensitivity but poor specificity for diagnosing chronic pancreatitis, and care must be taken before basing the diagnosis only on EUS criteria
    - Parenchymal features
    - Ductal features

TABLE 4. EUS diagnosis of CP on the basis of consensus criteria*

I. Consistent with CP

A. 1 major A feature (+) ≥3 minor features

B. 1 major A feature (+) major B feature

C. 2 major A features

II. Suggestive of CP†

A. 1 major A feature (+) <3 minor features

B. 1 major B feature (+) ≥3 minor features

C. ≥5 minor features (any)

III. Indeterminate for CP†

A. 3 to 4 minor features, no major features

B. major B feature alone or with <3 minor features

IV. Normal

≤2 minor‡ features, no major features

*EUS diagnosis of CP should be made in the appropriate clinical setting.
†Diagnosis requires confirmation by additional imaging study (ERCP, CT, MRI, or PFT).
‡Excludes cysts, dilated MPD, hyperechoic nonshadowing foci, dilated side branch.

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Catalano et al. Gastrointestinal Endoscopy. Volume 69, No. 7 : 2009

Investigation

TABLE 2. Consensus-based parenchymal features of CP

Feature	Definition	Major criteria	Minor criteria	Rank	Histologic correlation
Hyperechoic foci with shadowing	Echogenic structures ≥2 mm in length and width that shadow	Major A		1	Parenchymal-based calcifications
Lobularity	Well-circumscribed, ≥5 mm structures with enhancing rim and relatively echo-poor center			2	Unknown
A. With honeycombing	Contiguous ≥3 lobules	Major B			
B. Without honeycombing	Noncontiguous lobules		Yes		
Hyperchoic foci without shadowing	Echogenic structures foci ≥2 mm in both length and width with no shadowing		Yes	3	Unknown
Cysts	Anechoic, rounded/elliptical structures with or without septations		Yes	4	Pseudocyst
Stranding	Hyperechoic lines of ≥3 mm in length in at least 2 different directions with respect to the imaged plane		Yes	5	Unknown

Attendees ranked these features according to predictive value (1 = hig

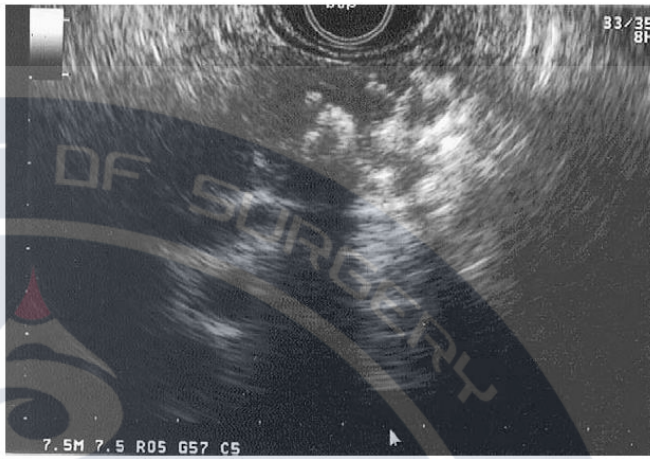

Figure 3. Hyperechoic foci with shadowing within the parenchyma.

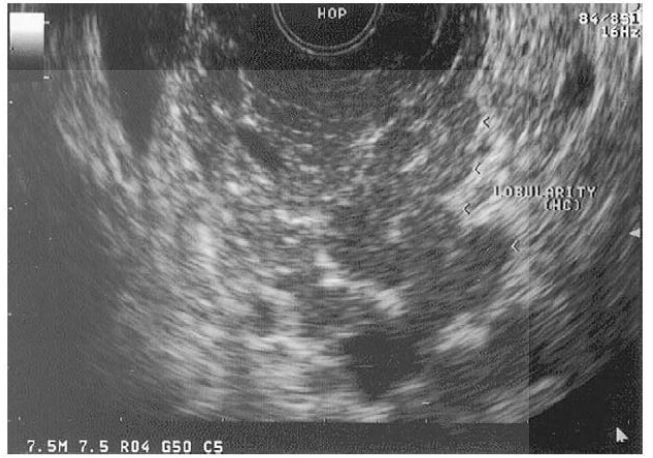

Figure 4. Pancreatic parenchyma demonstrating honeycombing lobularity.

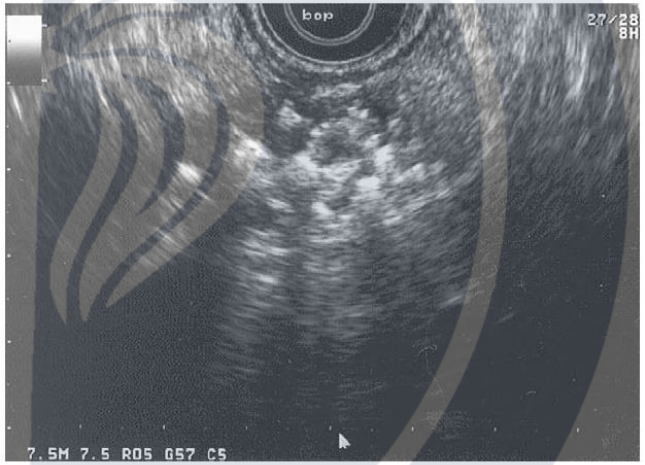

Figure 5. Nonshadowing hyperechoic foci within the parenchyma.

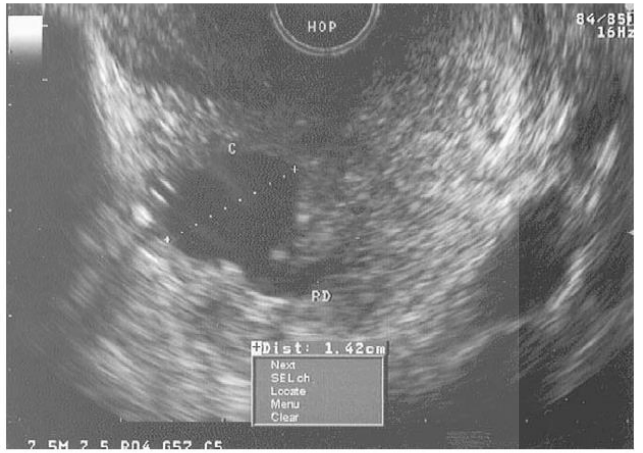

Figure 6. Pancreatic cyst *(c)* measuring 1.4 cm, communicating with the PD.

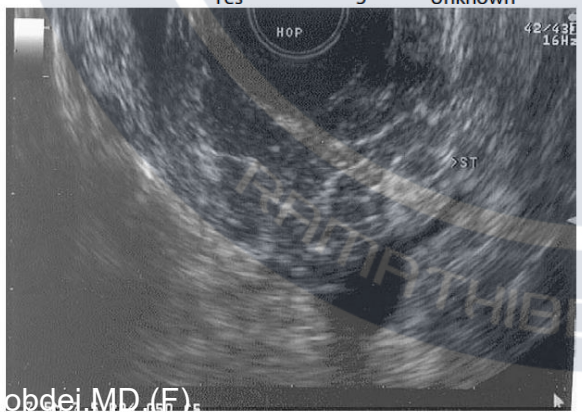

Figure 7. Pancreatic parenchyma with stranding (hyperechoic lines >3 mm in multiple directions).

- Parenchymal features

Catalano et al. Gastrointestinal Endoscopy. Volume 69, No. 7 : 2009

Investigation

- Ductal features

TABLE 3. Consensus-based ductal features of CP

Feature	Definition	Major criteria	Minor criteria	Rank	Histologic correlation
MPD calculi	Echogenic structure(s) within MPD with acoustic shadowing	Major A		1	Stones
Irregular MPD contour	Uneven or irregular outline and ectatic course		Yes	2	Unknown
Dilated side branches	3 or more tubular anechoic structures each measuring ≥1 mm in width, budding from the MPD		Yes	3	Side-branch ectasia
MPD dilation	≥3.5-mm body or >1.5-mm tail		Yes	4	MPD dilation
Hyperechoic MPD margin	Echogenic, distinct structure greater than 50% of entire MPD in the body and tail		Yes	5	Ductal fibrosis

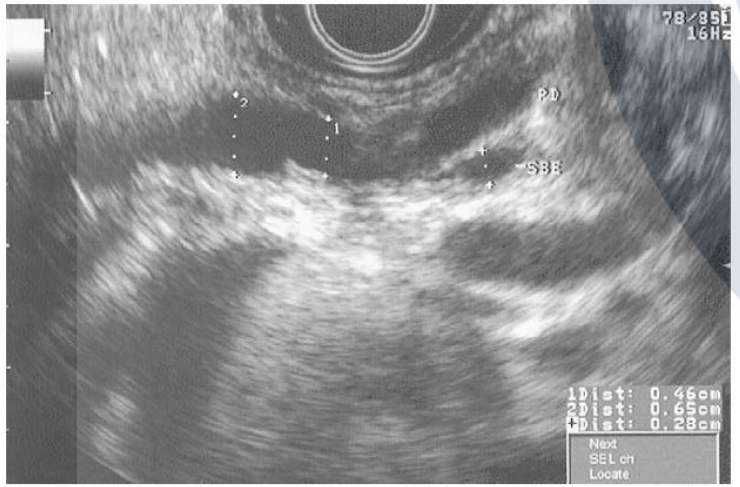

Figure 10. EUS image demonstrating a dilated PD measuring 0.65 cm (F) with side-branch ectasia measuring 0.28 cm.

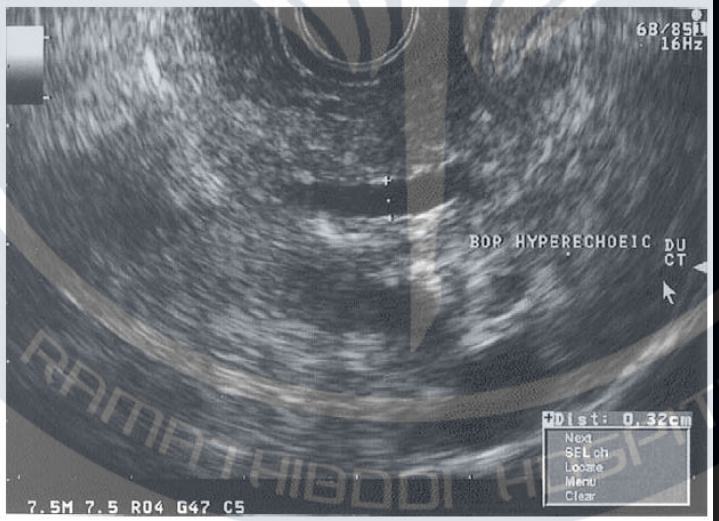

Figure 11. PD demonstrating hyperechoic borders.

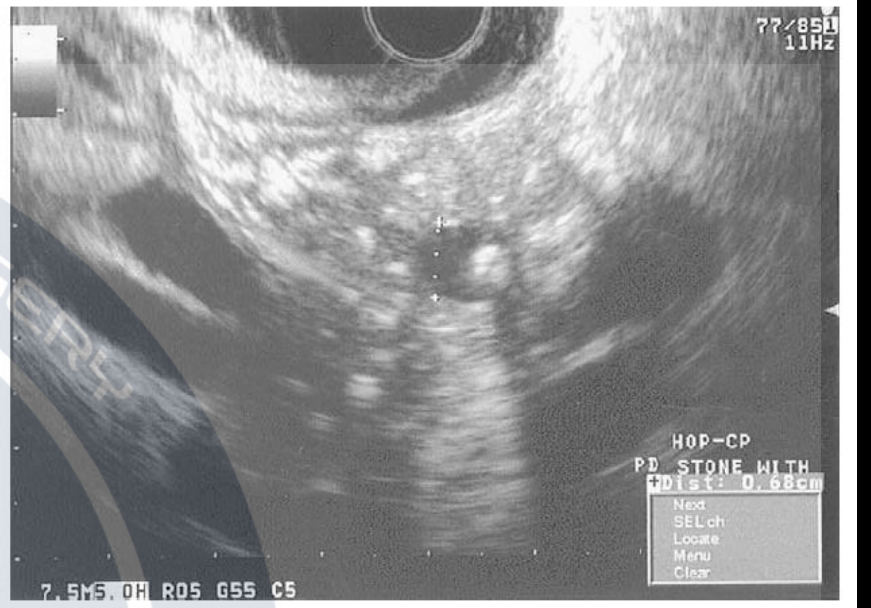

Figure 8. Dilated pancreatic duct (0.68 cm) with MPD calculi with shadowing.

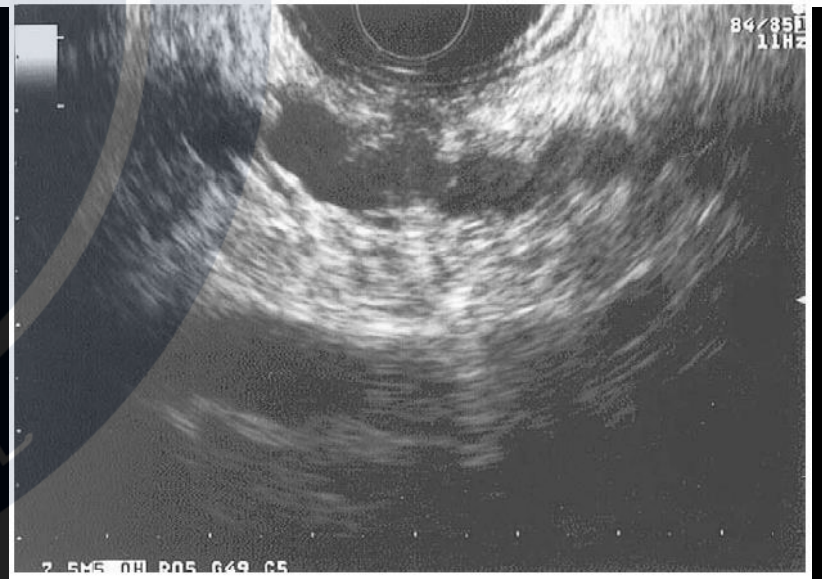

Figure 9. Dilated PD with marked contour irregularity.

Catalano et al. Gastrointestinal Endoscopy. Volume 69, No. 7 : 2009

Investigation

Table S2*: Estimated overall sensitivity, specificity, and heterogeneity per imaging modality

Modality	No. of studies	No. of patients	Sensitivity (95%CI)	Specificity (95%CI)	Heterogeneity (I^2)
EUS	15	1181	82% (71%-90%)	91% (83%-95%)	82% / 75%
MRCP	14	933	78% (69%-85%)	96% (90%-98%)	59% / 65%
ERCP	11	742	82% (76%-87%)	94% (87%-98%)	39% / 67%
CT	10	700	75% (66%-83%)	91% (81%-96%)	50% / 71%
US	10	1005	67% (53%-78%)	98% (89%-100%)	40% / 93%

Random effects model. *from (2)

Lo¨hr et alUnited European Gastroenterology Journal 2017, Vol. 5(2) 153–199

Investigation

- Test of exocrine pancreatic dysfunction
  - Minor, complementary role in the diagnosis of chronic pancreatitis
    - High sensitivity only in advanced stages of chronic pancreatitis
    - Low clinical availability of most direct tests
    - Utility of function tests is limited to the diagnosis of more advanced disease
    - Low specificity (70%)

BLUMGART'S Surgery *of the* Liver, Biliary Tract and Pancreas. 7th ed. 2023

Investigation

- Test of exocrine pancreatic dysfunction
  - Invasive (Direct) pancreatic function test
    - Duodenal intubation and aspiration of duodenal juice after pancreatic stimulation
    - Secretin stimulation test -> Detection of functional impairment in all stages of chronic pancreatitis (sensitivity and specificity between 75% and 95%)
  - Non-invasive (Indirect) pancreatic function test
    - Measuring the absorption of some compound (e.g., fat), which first requires digestion by pancreatic enzymes
    - Measuring the level of enzymes or zymogens secreted by the pancreas (serum trypsinogen or fecal elastase [FE-1])

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Table 4. Test characteristics of direct and indirect pancreatic function tests (110,111)

Test	Advantages	Disadvantages
Hormonal tests of pancreatic function		
CCK stimulation test (acinar cell stimulation measuring trypsin and/or lipase)	Direct acinar cell function Detects subtle EPI	Cumbersome Not widely available Specialized laboratory testing required Patient discomfort with Dreiling tube placement 2–3 hr test
Secretin stimulation test (ductal cell stimulation measuring bicarbonate)	Direct ductal cell function Performed endoscopically Uses laboratory autoanalyzer 60 min test Measures ductal secretory ability	Not widely available Prone to measurement error Risk and cost of endoscopy
Nonhormonal tests of pancreatic function		
Fecal elastace-1	Universally available Easily obtainable Noninvasive	Moderate sensitivity Limited specificity in diarrhea Limited use in mild disease
^{13}C-mixed triglyceride test	Easily obtainable High sensitivity (90%)	Not universally available Long test duration—4–6 hr
Serum trypsinogen/trypsin	Universally available Easily obtainable Noninvasive Quantifiable for tracking function over time	Does not measure digestive tract enzymes Elevated with pancreatic pain

CCK, cholecystokinin; EPI, exocrine pancreatic insufficiency.

Gardner et al. ACG Clinical Guideline: Chronic PancreatitisAm J Gastroenterol 2020;115:322–339.

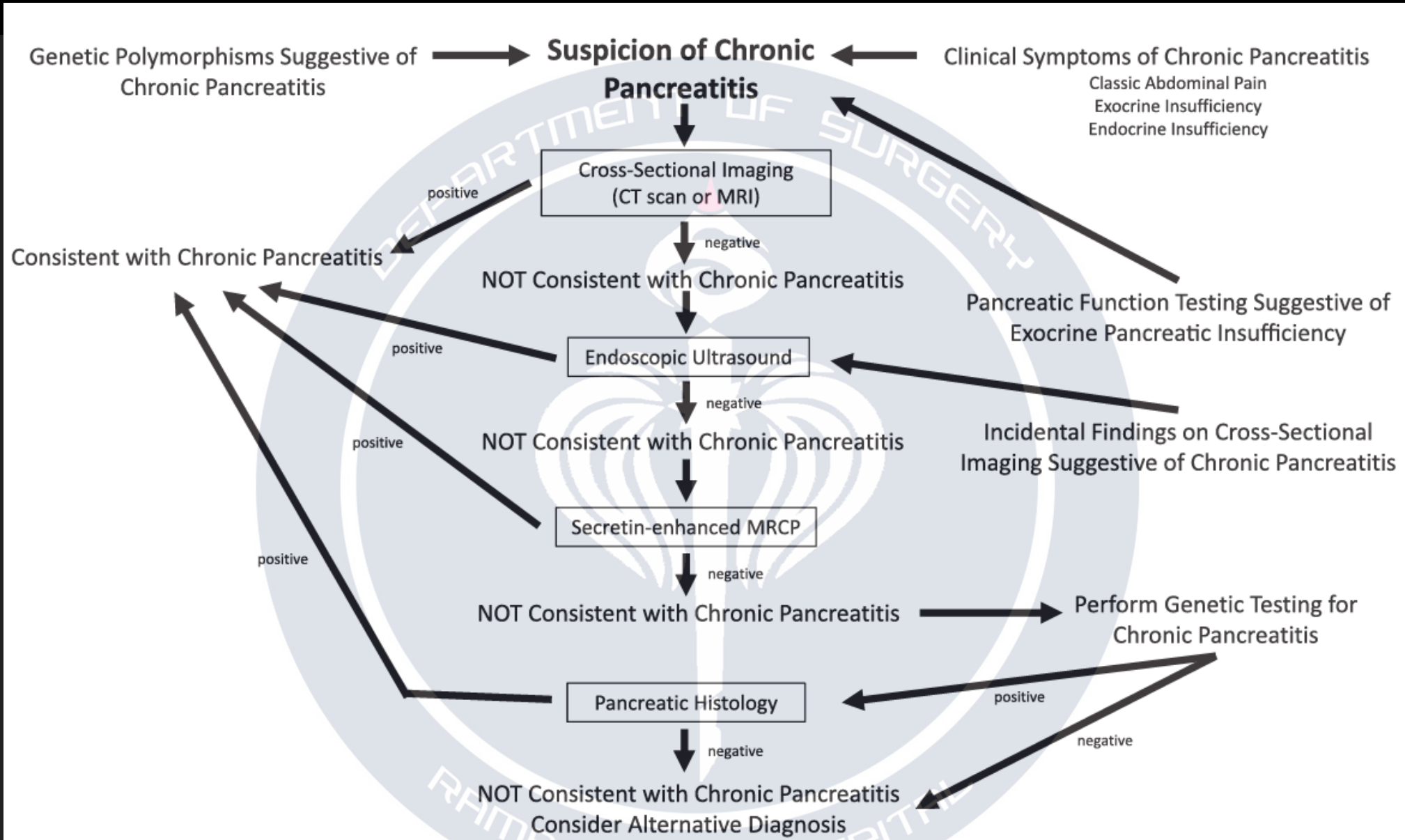


Figure 1. Diagnostic algorithm for chronic pancreatitis (CP) based on the clinicopathologic disease model of CP. This algorithm uses a symptom-first approach to diagnosis and does not stratify based on the etiology of disease or clinical risk factors. CT, computed tomography; MRCP, magnetic resonance cholangiopancreatography.

Gardner et al. ACG Clinical Guideline: Chronic PancreatitisAm J Gastroenterol 2020;115:322–339.

Management

- Medical Treatment
- Endoscopic Treatment
- Surgical Treatment

Medical Treatment

- Lifestyle Modification
  - Alcohol cessation
    - Reduction of recurrent pancreatitis
  - Smoking cessation
- Antioxidant therapy
  - Oxidative stress as a mechanism of inflammation in CP
    - Ameliorate oxidative stress and relieve pain
  - Combination of antioxidants (b-carotene, vitamin C, vitamin E, selenium, and methionine) has shown significant pain relief while studies with single antioxidant therapy showed no significant pain relief
- PERT – no effects to chronic pancreatic pain

A.M. Drewes et al. Pancreatology 17 (2017) 720-731
Lo¨hr et al.United European Gastroenterology Journal 2017, Vol. 5(2) 153–199

Medical Treatment

Pain control

- Standard guideline for analgesic therapy in CP follows the principles of the “pain relief ladder” provided by WHO
  - Level I : Paracetamol – due to its limited side effects
    - NSAIDs should in general be avoided due to their gastrointestinal toxicity - CP patients are predisposed to peptic ulcers
  - Level II : Weak opioid such as Tramadol
    - Shown to be superior to morphine in chronic pancreatitis
  - Level III : Strong opioid such as morphine
    - High risk of dependency and side effects

A.M. Drewes et al. Pancreatology 17 (2017) 720-731
Lo¨hr et al.United European Gastroenterology Journal 2017, Vol. 5(2) 153–199

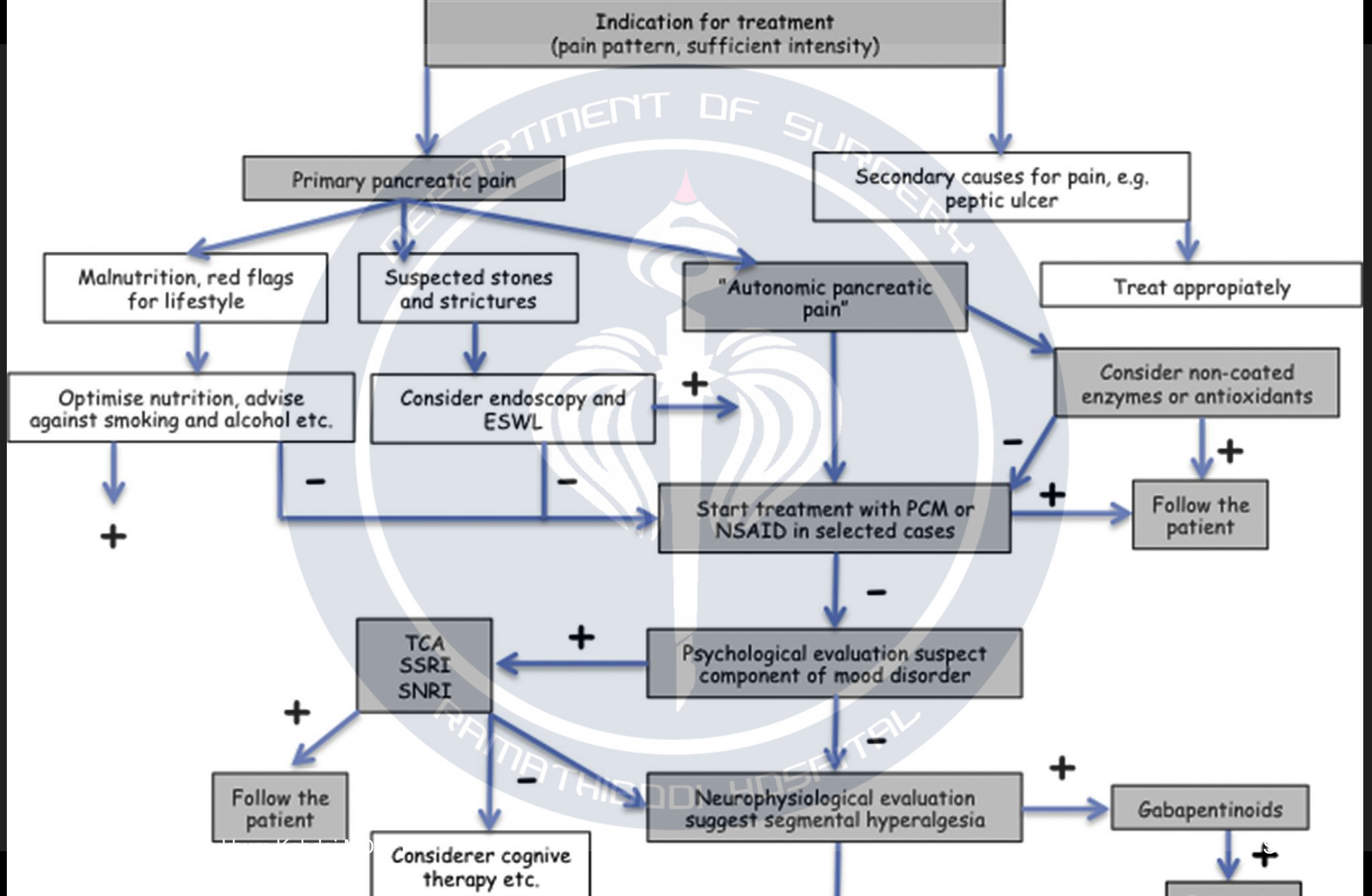
Medical Treatment

Pain control

- Adjuvant analgesics
  - Heterogeneous group of drugs initially developed for indications other than pain and include antidepressants, anticonvulsants as well as anxiolytics
- Anti-depressive drugs
  - Pain treatment in functional visceral pain disorders and although no data exist in CP, their positive effects in patients with neuropathic pain
- Gabapentinoid, pregabalin, has been investigated in a placebo-controlled randomised trial and was found to induce moderate pain relief with relatively limited side effects

A.M. Drewes et al. Pancreatology 17 (2017) 720-731

Lo¨hr et al.United European Gastroenterology Journal 2017, Vol. 5(2) 153–199


Indication for treatment
(pain pattern, sufficient intensity)
Primary pancreatic pain
Secondary causes for pain, e.g. peptic ulcer
Malnutrition, red flags for lifestyle
Suspected stones and strictures
"Autonomic pancreatic pain"
Treat appropiately
Optimise nutrition, advise against smoking and alcohol etc.
Consider endoscopy and ESWL
Consider non-coated enzymes or antioxidants
Start treatment with PCM or NSAID in selected cases
Follow the patient
TCA
SSRI
SNRI
Psychological evaluation suspect component of mood disorder
Follow the patient
Considerer cognive therapy etc.
Neurophysiological evaluation suggest segmental hyperalgesia
Gabapentinoids

Medical Treatment

- ACG 2020
  - Opiates may be considered to treat painful CP only in patients in whom all other reasonable therapeutic options have been exhausted
  - Due to risk of addiction, abuse, and tolerance as well as concerns about providing patients who may already have a history of substance abuse
  - Justified for refractory pain

Medical Treatment

- Diabetes mellitus type 3c
  - Fulfillment of the diagnostic criteria for DM
  - Fulfillment of diagnostic criteria for CP
  - Exclusion of other potential sources of DM

Endocrine insufficiency - Diabetes mellitus type 3c

- 80% of chronic pancreatitis will develop DM
  - A couple of decades after the onset of symptoms
- Pathophysiology
  - Insulin deficiency secondary to acinar cell fibrosis, which results in reduced insulin production
  - Some study showed beta cell dysfunction mediated by pro-inflammatory cytokines and development of both hepatic and peripheral insulin resistance
  - Maldigestion of nutrients secondary to EPI -> Impaired effect of two key incretin hormones [glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1)]
- Frequent screening for DM is recommended due to high prevalence
- Insulin is often considered for 1st line treatment
- Metformin is another considerable option for mild severity

Ramsey et al. Dig Dis Sci. 2017 July ; 62(7): 1745–1750

Medical Treatment

Exocrine pancreatic insufficiency

- Consequence of inadequate production and/or secretion of pancreatic enzymes
  - Disruption of the normal production, storage, and/or secretion of pancreatic enzymes
- Symptoms of mild EPI are mostly related to fat malabsorption and include abdominal bloating, cramping, and gas
- Symptoms of severe EPI include unexplained weight loss and steatorrhea
  - Steatorrhea, indicating clinically significant fat malabsorption, does not develop until approximately 90% of the exocrine pancreatic function is lost
- Develop more than 10 years after symptom onset

Ramsey et al. Dig Dis Sci. 2017 July ; 62(7): 1745–1750

Medical Treatment

Exocrine pancreatic insufficiency

- Assessed with pancreatic function test (direct – indirect test)
- Initiation of PERT is recommended to reduce symptoms and normalize nutrient absorption
  - Suggest a starting dose of 25,000–50,000 units of lipase per meal with titration based on resolution of symptoms and nutritional deficien
  - Take 50% of their mealtime dose with snacks
- EPI, not responsive to PERT
  - Further titration of PERT dosage
  - Addition of a proton pump inhibitor
  - Empiric therapy for bacterial overgrowth or bile salt diarrhea

Ramsey et al. Dig Dis Sci. 2017 July ; 62(7): 1745–1750

Medical Treatement

Metabolic Bone Disease

- Chronic pancreatitis related osteopathy : includes either osteopenia or osteoporosis, prevalence : approximately 66%
- Multiple factors
  - Shared risk factors (e.g., cigarette smoking, excessive alcohol usage)
  - Vitamin D deficiency
  - Chronic inflammation, which promotes an imbalance of bone production and resorption that favors bone loss
- No societal guidelines to recommend screening for metabolic bone disease in CP
  - Baseline screening for patients with CP can be justified
- Clinical management is similar to the management of metabolic bone disease in the general population
  - Abstinence from alcohol and tobacco, and increased weight-bearing physical activity
  - Diet rich in calcium and vitamin D
  - Pharmacologic supplementation : bisphosphonates

Ramsey et al. Dig Dis Sci. 2017 July ; 62(7): 1745–1750

Endoscopic Treatment

- Based on the rationale that pain is related to an outflow obstruction of the MPD due to stricture or pancreatic intraductal stone
  - ERCP : MPD drainage by sphincterotomy of the major and/or minor papilla
  - Short-term stent placement or by pancreatic stone extraction, usually after fragmentation with ESWL
- No role in asymptomatic and uncomplicated CP
- Usually performed first in most cases, with surgery reserved to the fail endoscopic patients
  - The efficacy of ET has been found to be lower compared with surgery
- Pre-treatment factors for best responders
  - Location of obstructing stones in the head of the pancreas, the absence of MPD stricture, a short disease duration and a low frequency of pain attacks before ET

A.M. Drewes et al. Pancreatology 17 (2017) 720-731
Lo¨hr et al.United European Gastroenterology Journal 2017, Vol. 5(2) 153–199

Endoscopic Treatment

Pancreatic duct stricture

- Defined as strictures with an upstream MPD dilation 6 mm in diameter or strictures that prevent the outflow of contrast medium
- Stricture dilation alone is not recommended, temporary plastic stenting is more preferred
- Dominant MPD strictures located in the head of the pancreas and associated with pain
  - Single plastic stenting (10Fr) for at least 12 months with at least one planned stent exchange within one year
  - Criteria for not replacing a temporary plastic stent after removal
    - Adequate contrast medium outflow in the duodenum and easy passage of a 6 Fr catheter through the residual dilated stricture

Lo¨hr et alUnited European Gastroenterology Journal 2017, Vol. 5(2) 153–199

The ASGE Standards of Practice Committee. Gastrointestinal Endoscopy Volume 100, No. 4 : 2024

Endoscopic Treatment

Pancreatic duct stricture

- ASGE recommend placement of single, largest possible diameter plastic stent
  - Avoid forceful or traumatic placement with gradual upsizing if necessary
  - Assess the need for upsizing the stent at 3 monthly follow-up ERCPs after the initial PS placement
  - Against the use of FCSEMS due to high risk of adverse events and questionable efficacy
- Refractory MPD strictures
  - Defined as persistent symptomatic dominant strictures after one year of single stent placement
  - Multiple pancreatic duct stenting for treating a refractory MPD stricture
  - Trial of 3–6 months with FC-SEMS
  - Surgical pancreaticojejunostomy

Lo¨hr et alUnited European Gastroenterology Journal 2017, Vol. 5(2) 153–199
The ASGE Standards of Practice Committee. Gastrointestinal Endoscopy Volume 100, No. 4 : 2024

Endoscopic Treatment

Pancreatic duct stone

- Removal of stones at endoscopy may relieve obstruction and improve pain
  - Conventional ERCP alone (with interventions including stricture dilation, stent placement, or stone extraction alone or in combination)
    - Successful in less than 15% of CP patients
    - Reserved for smaller stones (<5 mm) or radiolucent stones that cannot be targeted by ESWL and typically located in the head, neck, and body of the pancreas
  - ESWL
    - Requires a clear shock wave pathway without interference by bones, calcified vessels, or lung tissue, with most patients requiring 3 ESWL sessions for stone clearance
  - Pancreatoscopy with electrohydraulic lithotripsy (EHL)
    - Non-radiopaque stones unable to be seen on fluoroscopy can be fragmented under direct vision and the procedure can be combined with ERCP at the same time
    - Technically difficult when stones are located upstream from a PD stricture or in the tail of the pancreas

The ASGE Standards of Practice Committee. Gastrointestinal Endoscopy Volume 100, No. 4 : 2024

Endoscopic Treatment

Pancreatic duct stone

- Management strategy be based on stone size, location, and radiopacity
- ESWL can be considered as first step treatment for larger, radiopaque stones (5 mm) obstructing the MPD -> followed by the endoscopic extraction of stone fragments
  - ESWL alone may be a more cost-effective option
  - Non-contrast CT before ESWL can determine the location, size, number and density of stones
- Radiopaque PD stones >5 mm -> either pancreatoscopy with lithotripsy or ESWL can be used depending on local availability
- Pancreatoscopy with lithotripsy may be more efficient than ESWL in ductal clearance except when stones are >10 mm

Lo¨hr et alUnited European Gastroenterology Journal 2017, Vol. 5(2) 153–199

Endoscopic Treatment

In patients with painful CP and main PD stones, the ASGE suggests that the management strategy be based on stone size, location, and radiopacity:

a. For radiopaque stones >5 mm and in the head, neck, or body of the pancreas, the ASGE suggests ERCP with or without pancreatoscopy or ESWL alone.
b. After ESWL and with no spontaneous stone clearance after adequate fragmentation (defined as the presence of fragments <2-3 mm), the ASGE suggests performing ERCP (with or without pancreatoscopy) for stone clearance.
c. For radiopaque stones <5 mm, any radiolucent stone, or contraindications to ESWL, the ASGE suggests ERCP with or without pancreatoscopy.

(Conditional recommendation/very low to low quality of evidence)

- The decision to choose pancreatoscopy or ESWL is largely based on local expertise and availability of these modalities.
- Consider ESWL for radiopaque stones >10 mm.
- Pancreatoscopy is likely to be difficult in the presence of strictures, with stones upstream from the stricture.

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Endoscopic Treatment

Pancreatic duct stone

- Complications of ESWL
  - Pancreatitis**
  - Skin erythema
  - Haematuria
  - Gastrointestinal bleeding
  - ‘Steinstrasse’ (acute stone incarceration in the papilla responsible for MPD dilatation)
  - Hepatic subcapsular haematoma
  - Perforation
- ESWL : At long-term, pain relapses requiring analgesics or more invasive treatment : 5–45%

Lo¨hr et alUnited European Gastroenterology Journal 2017, Vol. 5(2) 153–199

Endoscopic Treatment

CBD stricture

- Increased risk of developing fibrotic strictures of the intrapancreatic portion of the common bile duct, which may occur in up to 25% of those with calcific CP
- Obstruction may be reversible because of acute inflammation
  - If persisting beyond 4 weeks, it should be treated to prevent secondary biliary cirrhosis
- Biliary dilation on imaging, but normal liver tests -> followed clinically
  - Intervention is recommended for those with marked, unexplained elevation of the serum alkaline phosphatase and/or bilirubin levels
- Symptomatic strictures should be treated
  - Recurrent acute cholangitis, obstructive jaundice or persistent (>1 month) cholestasis
  - Benefit for patients comply with repeat ERCPs and who are at high surgical risk, present with portal hypertension or have local abdominal conditions contraindicating surgery

Ramsey et al. Dig Dis Sci. 2017 July ; 62(7): 1745–1750

The ASGE Standards of Practice Committee. Gastrointestinal Endoscopy Volume 100, No. 4 : 2024

Endoscopic Treatment

CBD stricture

- Temporary stenting of CBD strictures with multiple simultaneous plastic stents or covered SEMS provide long-term success in 90% of cases
  - ASGE suggests FCSEMSs over multiple PSs for the treatment of benign biliary strictures complicating CP
- Significant biliary obstruction resisting to biliary stenting-> surgical intervention
  - Hepaticojejunostomy or pancreaticoduodenectomy (which may be favored in patients with concurrent duodenal obstruction)

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Nerve Blockage

Celiac plexus block

- Provide pain relief and reduce narcotics use in patients with chronic pancreatitis
  - Neurolysis = bupivacaine + ethanol -> used in pancreatic cancer
  - Block = bupivacaine +/- triamcinolone
- The injection of ethanol, bupivacaine, and triamcinolone into the celiac plexus
  - Disrupts signal transmission to the spinal cord and central nervous system, theoretically interfering with the perception of pain
- Single treatment can potentially provide pain reduction or relief for 3–6 months
  - Less than 60% of patients get pain relief with an EUS-guided celiac plexus block, and it is nonsustained (<6 mo)
- Carefully considered in CP patients nonresponsive to medical therapy or when no endoscopic or surgical options are available (non-obstructive CP)
- May be considered in patients who have side effects to opioids or wish to avoid opioids

Fusaroli Pietro et al. Celiac plexus block for chronic pancreatitis… Endoscopy International Open 2015; 03: E60–E62
The ASGE Standards of Practice Committee. Gastrointestinal Endoscopy Volume 100, No. 4 : 2024

Nerve Blockage

Celiac plexus block

- Percutaneous celiac plexus block
- EUS guided celiac plexus block
  - Satisfactory reduction of abdominal pain in only 51% of patients
  - Safe, moderately effective, and repeatable treatment for patients with pain caused by chronic pancreatitis
  - Should be weighed against the alternative available options
- Responses from EUS guided is superior from percutaneous
  - ASGE recommend EUS guided over percutaneous guided CPB

Fusaroli Pietro et al. Celiac plexus block for chronic pancreatitis… Endoscopy International Open 2015; 03: E60–E62

The ASGE Standards of Practice Committee. Gastrointestinal Endoscopy Volume 100, No. 4 : 2024

Surgical Treatment

- Indication for surgery
  - Intractable pain
  - Suspicion of neoplasms
  - Local complication of adjacent organs such as duodenal or CBD stenosis, pseudoaneurysm or erosion of large vessels, large pancreatic pseudocysts and internal pancreatic fistula
- Drainage procedure
  - Surgical decompression of the pancreatic duct
  - Based on the assumption that dilated duct represents intraductal or pancreatic parenchymal hypertension and is possibly one of the main reasons for pain in CP
- Resection procedure
  - Inflammatory tumour of the pancreatic head is present in 30–50% of patients with CP
    - Postulated as one of the possible reasons for pain in CP, apart from that it can produce distal common bile duct stenosis, duodenal stenosis and MPD obstruction

M.A. Kempeneers et al. . Pancreatology 20 (2020) 149e157

A Perwaiz et al. Indian J Surg (January–February 2012) 74(1):47–54

Surgical Treatment

- Drainage procedure
  - Cystojejunostomy
  - Peustow operation
  - Modified Peustow operation
- Resection procedure
  - Whipple's operation
  - Duodenal-Preserving Pancreatic Head Resection(DPPHR)
    - Beger Procedure
    - Berne Procedure
  - Distal Pancreatectomy/Segmental Pancreatectomy
  - Total Pancreatectomy
    - Total pancreatectomy with islet cell autotransplant
- Mixed procedure
  - Frey Procedure
  - Izbicki Procedure

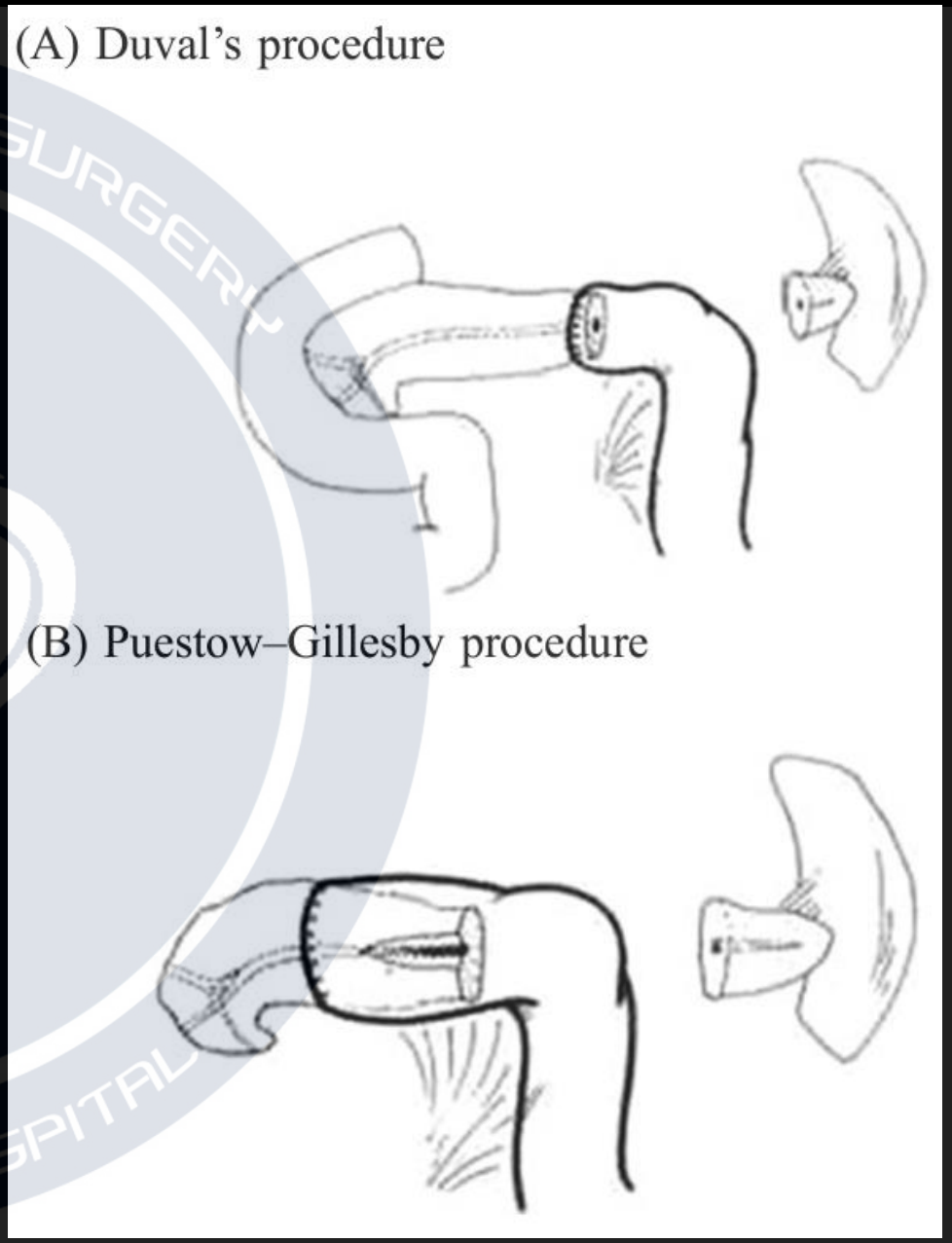
Table III
Consensus statement of the ISGPS – Reporting standards on operations for chronic pancreatitis

Domain 3: Standard operative descriptors
1. Longitudinal pancreaticjejunostomy[12]
2. Longitudinal pancreaticojejunostomy with partial pancreatic head resection[13]
3. Duodenum-preserving subtotal pancreatic head resection with transection at neck of pancreas[14]
4. Duodenum-preserving subtotal pancreatic head resection without transection at neck of pancreas[21]
5. Pancreatoduodenectomy
6. Total Pancreatectomy ± islet autotransplantation[22]
7. Distal pancreatectomy ± splenectomy

A.K. Siriwardena et al. . Surgery 168 (2020) 101-105

Drainage Procedure

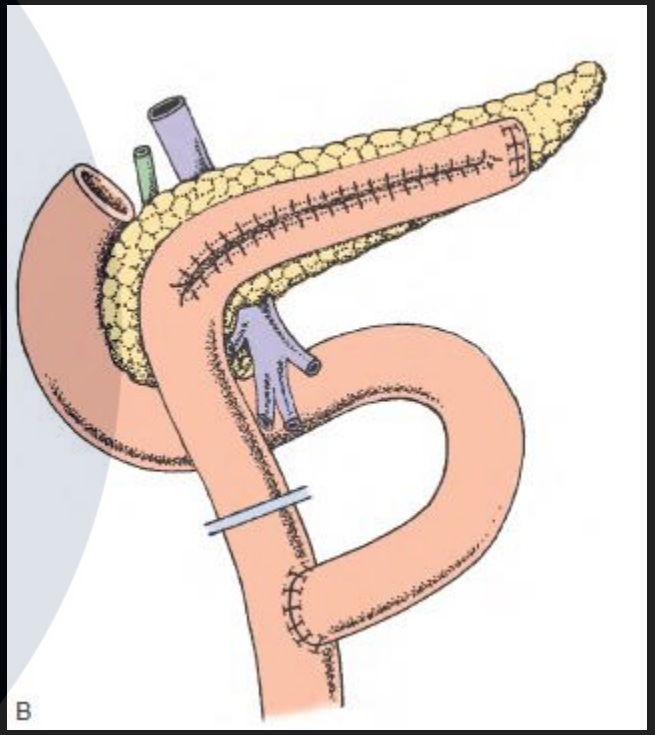
- Duval procedure
  - Distal pancreatectomy and splenectomy
  - Duct at the pancreatic tail was drained via an end-to-side pancreaticojejunostomy (PJ)
- Peustow operation
  - Modified Duval's procedure by adding longitudinal pancreaticojejunostomy (LPJ)
  - Aim to effectively drain the pancreatic duct even in the presence of multiple strictures or stones



A Perwaiz et al. Indian J Surg (January–February 2012) 74(1):47–54

Drainage Procedure

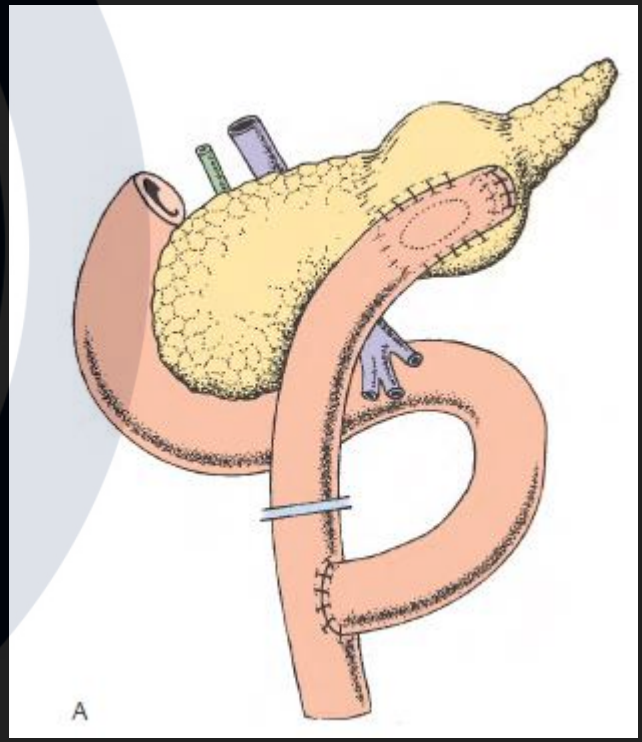
- Partington-Rochelle Procedure
  - Spleen-preserving longitudinal pancreaticojejunostomy without pancreatic tail resection
  - Mortality 3%, Morbidity 20%
  - Pancreatic tissue is preserved
    - Most patients : MPD can be effectively drained
    - Provide short-term pain relief in 75% of the patients
    - Frequently fails to provide long lasting pain relief
      - Persisting or recurrent pain : Incomplete decompression of the MPD ,especially in the head of the pancreas
  - Only suitable indication : Isolated dilatation of the pancreatic ductal (>7 mm) or “chain of lakes”, without an inflammatory mass in the pancreatic head



K. Bachmannetal.Best Practice & Research Clinical Gastroenterology.24(2010)299-310

Drainage Procedure

- Cystojejunostomy
  - Pseudocyst drainage after failure of endoscopic treatment is feasible
    - Only in symptomatic and complicated pseudocysts (pain or gastrointestinal discomfort caused by compression of the stomach, duodenum, or the proximal small bowel),
    - Not suitable or already treated with endoscopic approaches
  - Draining site should be located at the most caudal point of the cyst to ensure optimal drainage
  - Can be drained using transmesocolic approach in pseudocysts extending toward the transverse mesocolon
  - Long-term success rate of approximately 90%, and surgical morbidity and mortality are very low



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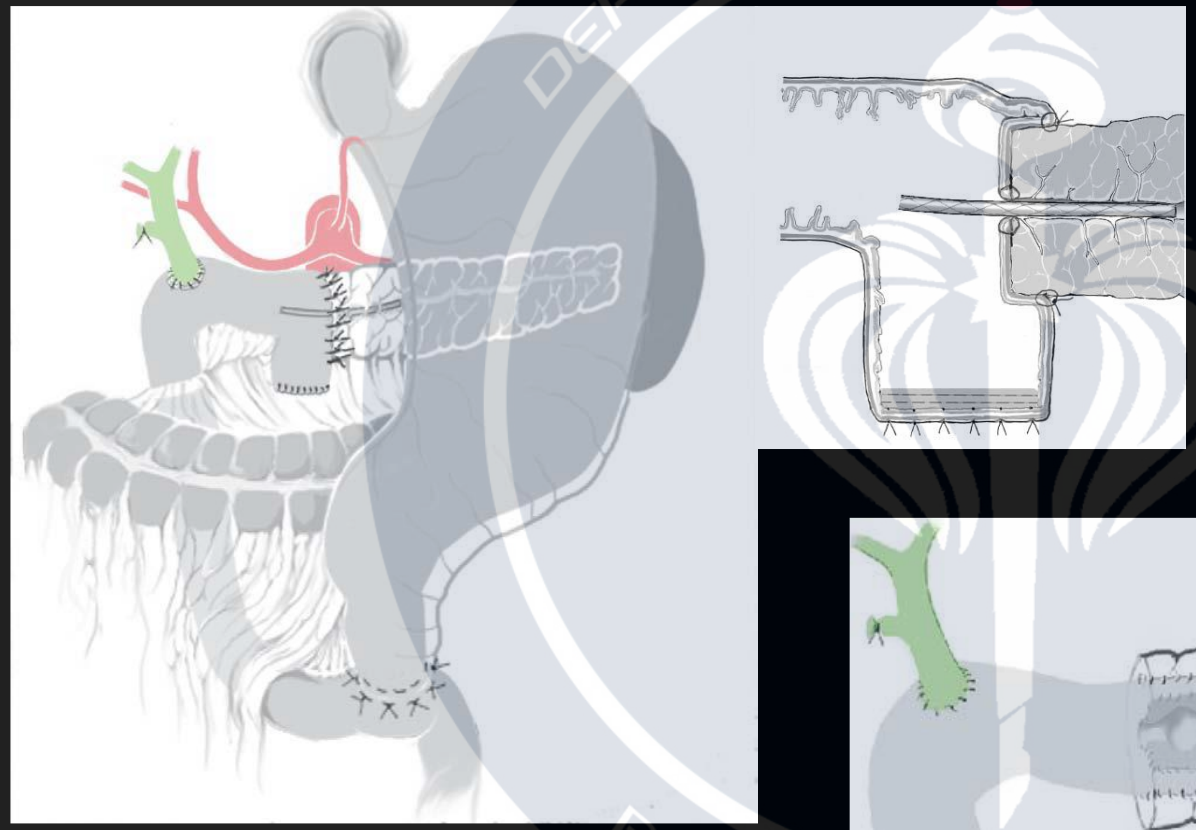
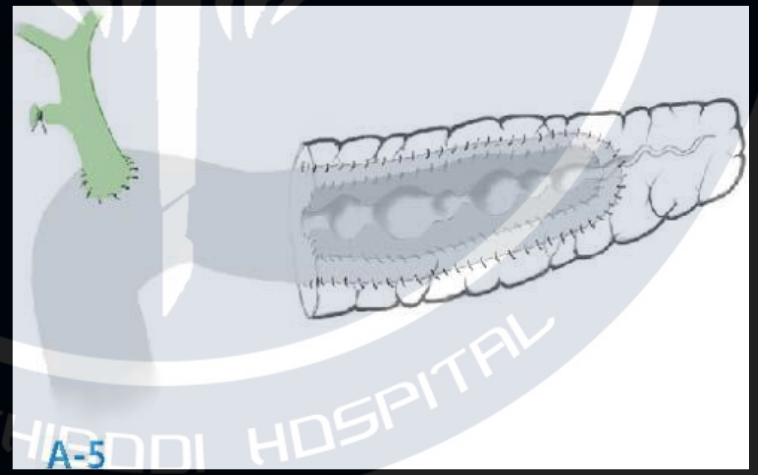
Resection Procedure

- Pancreaticoduodenectomy
  - Can be performed in classical Whipple operation or Pylorus preserving pancreaticoduodenectomy
  - Improve QoL and pain of short-long term in 90%
  - Disadvantage
    - Loss of surrounding non-diseased organs
    - Loss of natural bowel continuity
  - Mortality 0-5% with morbidity 20-40%

K. Bachmannetal.Best Practice & Research Clinical Gastroenterology.24(2010)299-310

Resection Procedure





- Side-to-side longitudinal technique can be used in chain-of-lakes-type ductal dilataion

Pierre-Alain Clavien et al. Atlas of Upper Gastrointestinal and Hepato-Pancreato-Biliary Surgery.2007

Resection Procedure

- Beger Procedure
  - Subtotal resection of the pancreatic head following the transsection of the pancreas above the portal vein
    - The pancreas is drained by an end-to-end or end-to-side pancreaticojejunostomy using a Roux-en-Y loop
  - Physiological gastroduodenal passage and common bile duct continuity are preserved
  - Provide pain relief in 75-95%
  - Mortality 0-3%, morbidity 15-32%

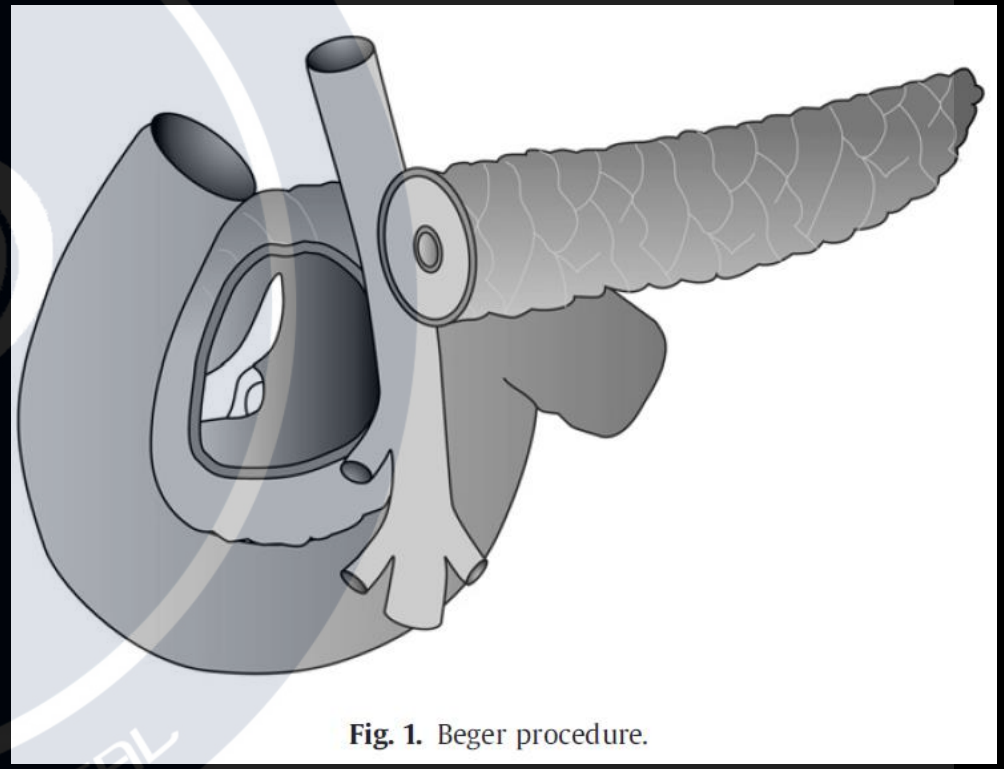
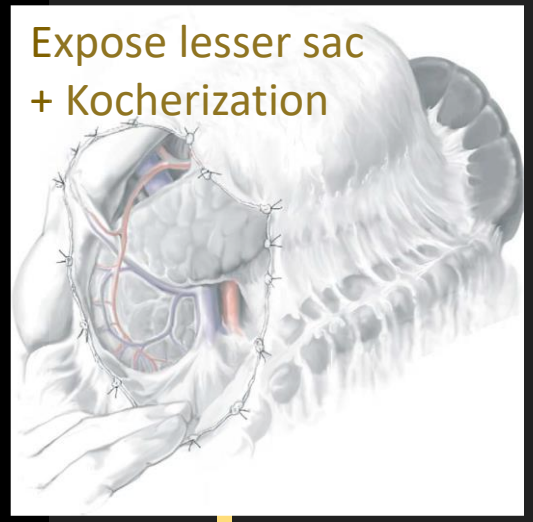


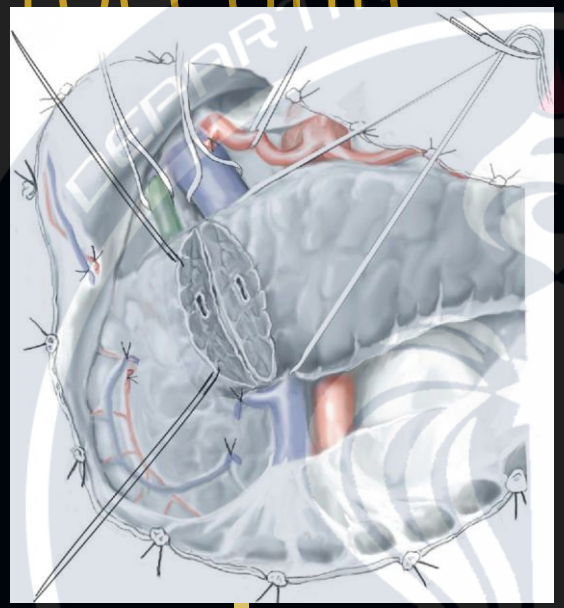
Fig. 1. Beger procedure.

K. Bachmannetal.Best Practice & Research Clinical Gastroenterology.24(2010)299-310

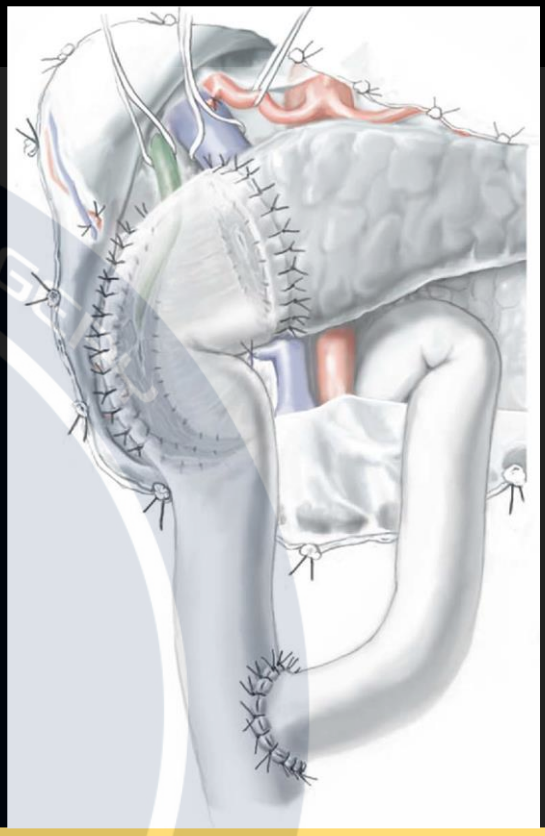
Resection Procedure

Expose lesser sac
+ Kocherization

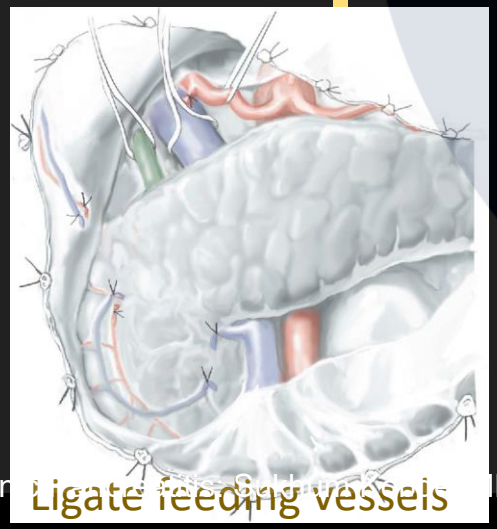




Transection of pancreatic neck

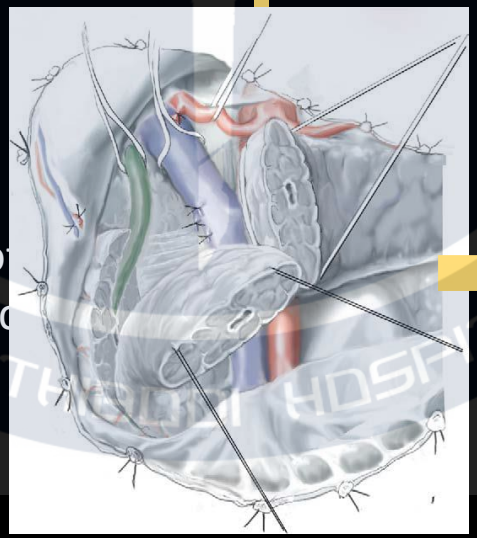


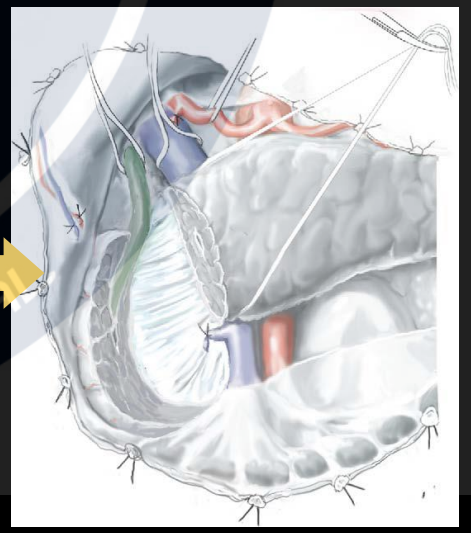
Anastomosis



Ligate feeding vessels

Subtotal excision of pancreatic head





Pierre-Alain Clavien et al. Atlas of Upper Gastrointestinal and Hepato-Pancreato-Biliary Surgery.2007

Resection Procedure

- Frey Procedure
  - Combine
    - Limited duodenum-preserving excision of pancreatic head
    - Longitudinal pancreaticojejunostomy of the body and tail of the pancreas : comparable to Partington-Rochelle procedure
  - No pancreatic transection, coring out head of pancreas
  - Low mortality <1%, Morbidity 9-39%
  - Operation is easier to Beger procedure; no transection of pancreas

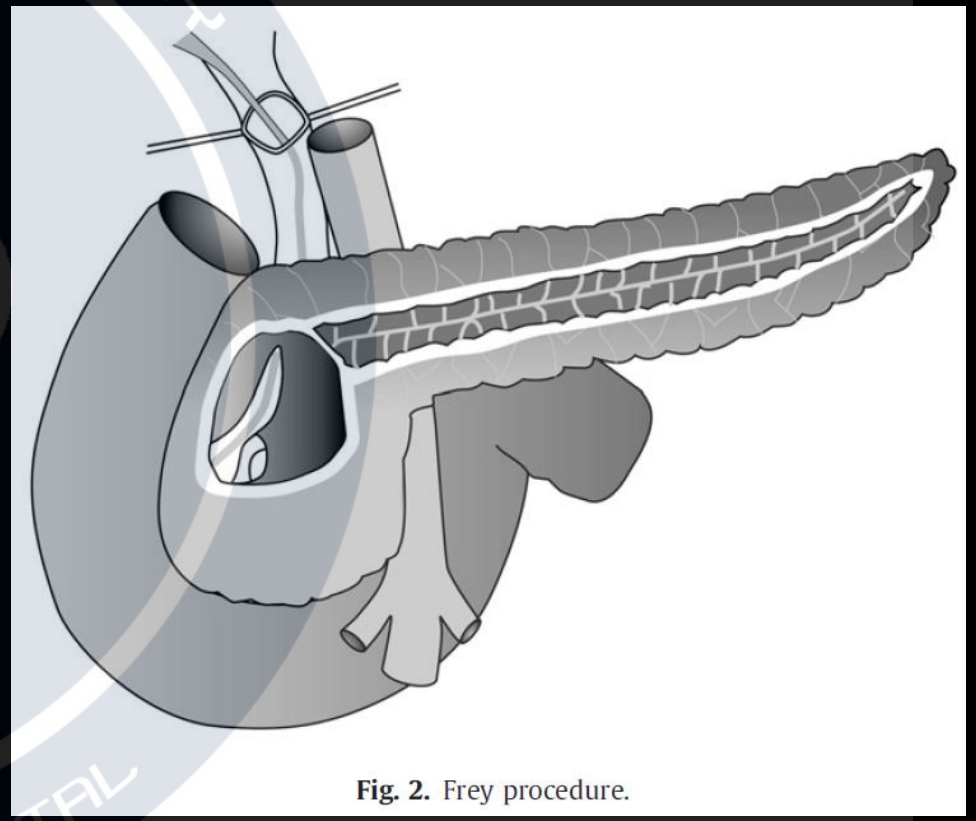
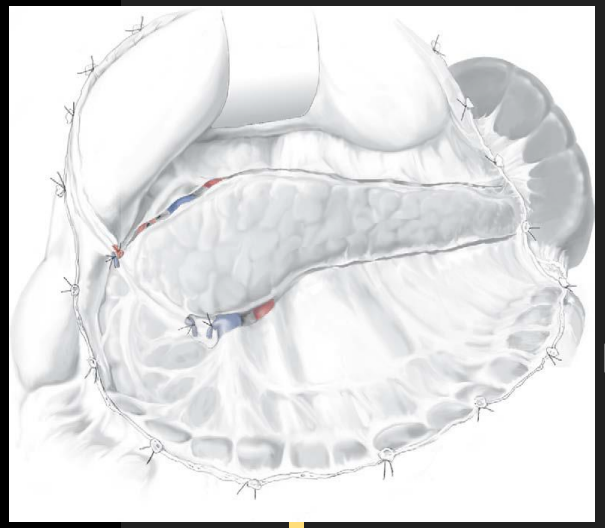


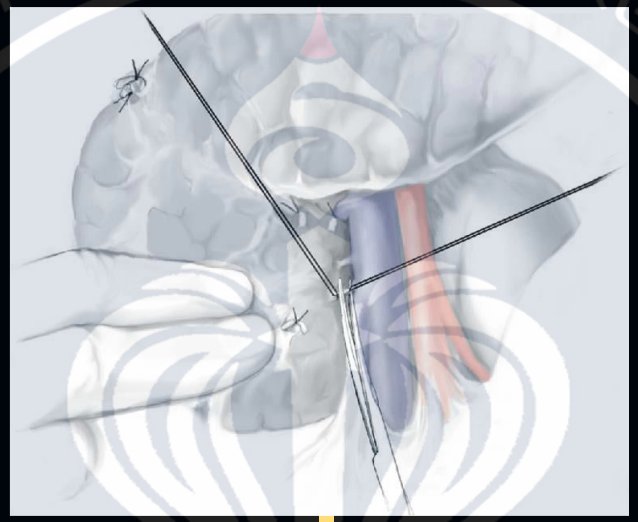
Fig. 2. Frey procedure.

K. Bachmannetal.Best Practice & Research Clinical Gastroenterology.24(2010)299-310

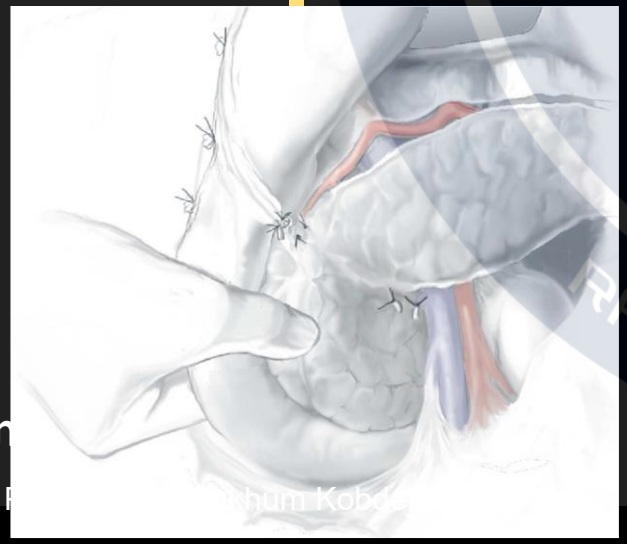
Resection Procedure



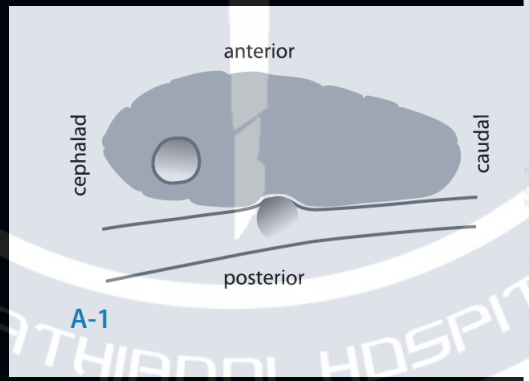
Expose lesser sac

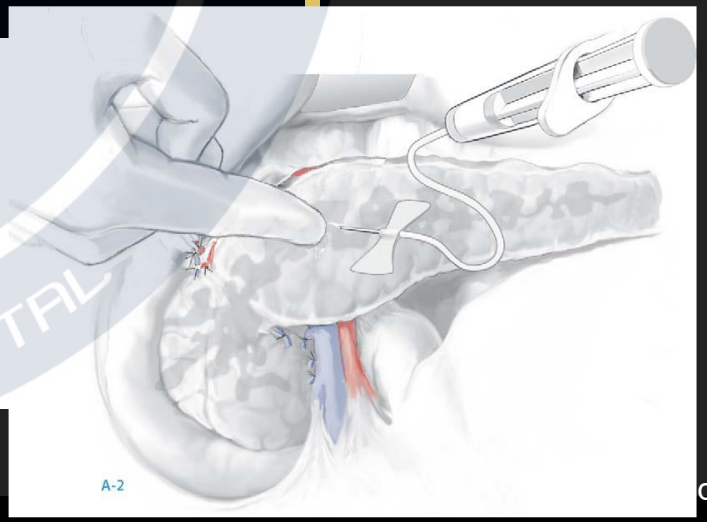


Dissection of head of pancreas from SMV
provide adequate rim of anastomosis



Kocherization





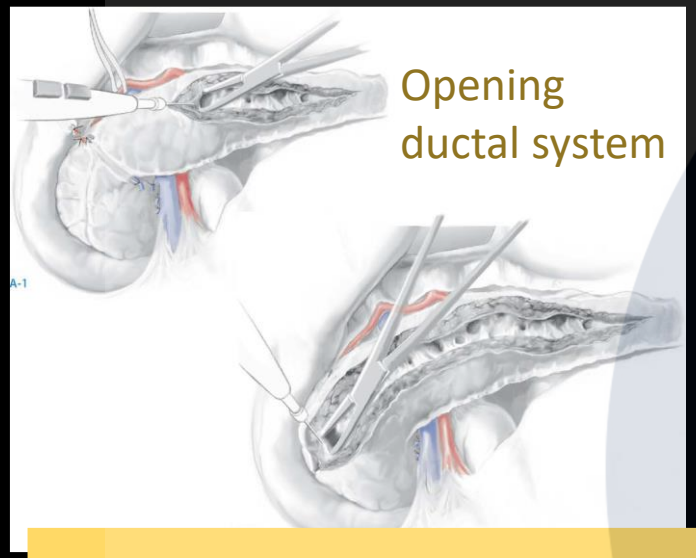
Identify
pancreatic
duct

Chronic P hum Kobold

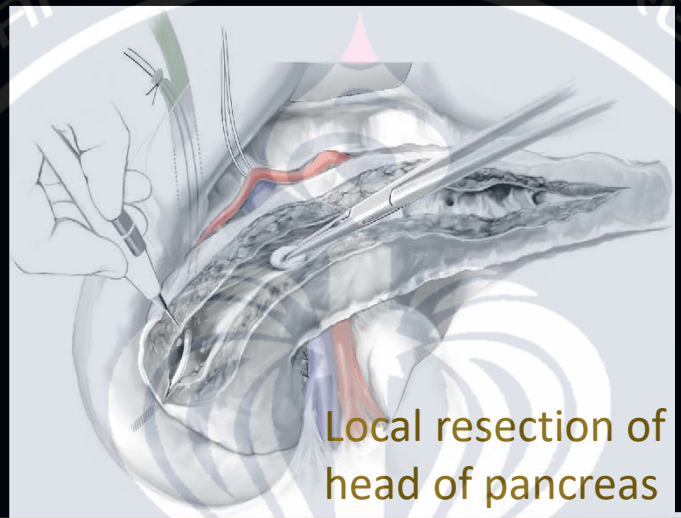
de 63/99

Pierre-Alain Clavien et al. Atlas of Upper Gastrointestinal and Hepato-Pancreato-Biliary Surgery.2007

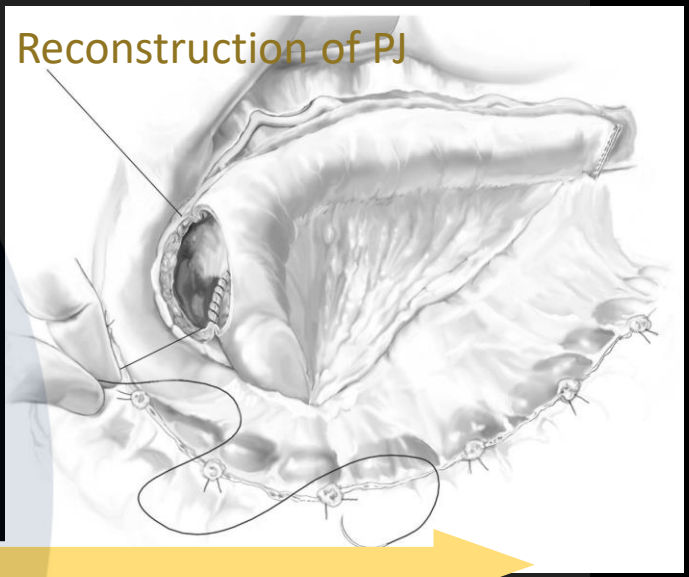
Resection Procedure



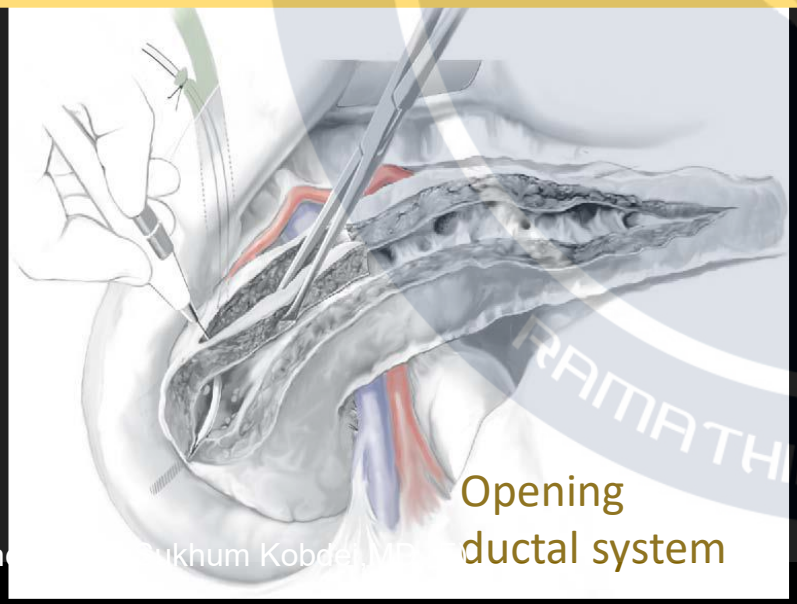
Opening
ductal system



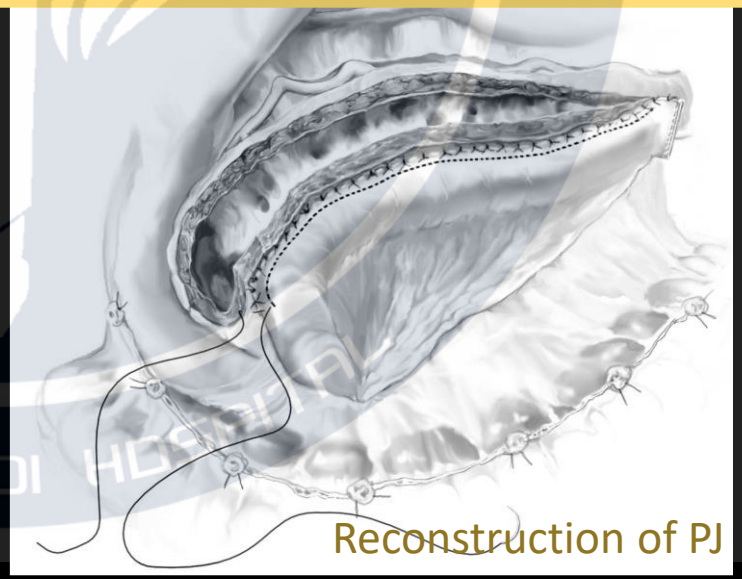
Local resection of
head of pancreas



Reconstruction of PJ



Opening
ductal system

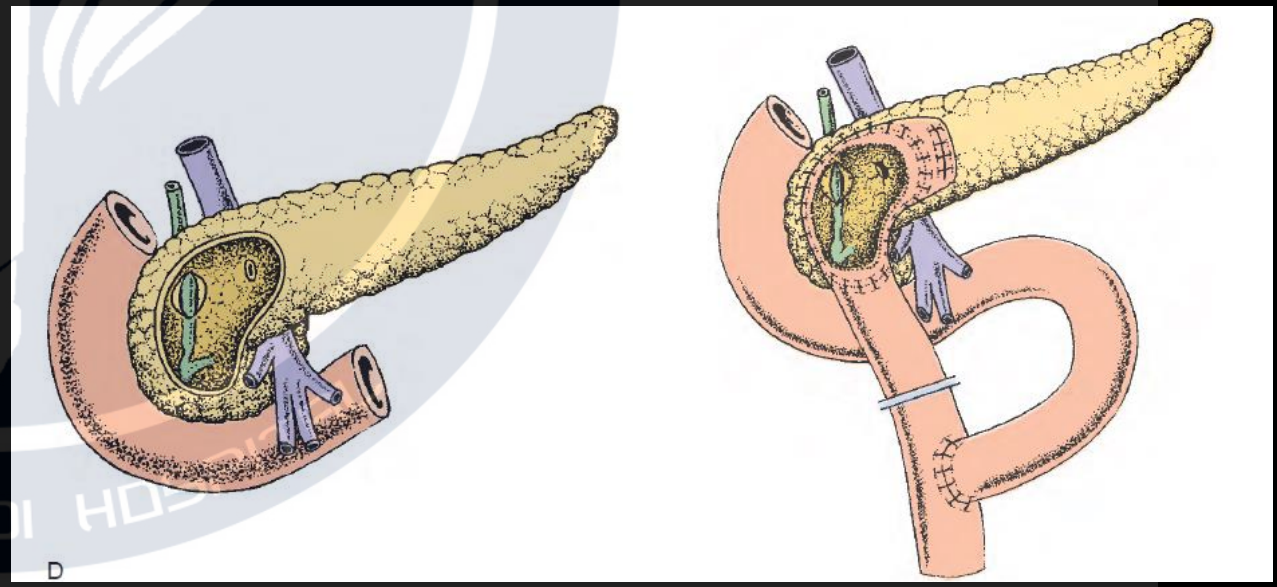


Reconstruction of PJ

Pierre-Alain Clavien et al. Atlas of Upper Gastrointestinal and Hepato-Pancreato-Biliary Surgery.2007

Resection Procedure

- Berne Procedure
  - Similar idea and combine Frey and Beger procedure
  - Avoids the delicate diversion of the pancreatic neck anterior to the PV
  - According to Berger's technique, a duodenum-preserving resection of the pancreatic head is performed.
  - Extent of pancreatic head excision is much larger compared to Frey procedure
    - Decompressing the common bile duct -> In CBD obstruction : longitudinal opening in the cavity of the pancreatic head is performed for bile drainage
    - Preventing a potential recurrence
    - No longitudinal drainage of the pancreatic as described by Frey and Izbicki is performed
  - Mortality of 0-1%, Morbidity 20-23%



K. Bachmannetal.Best Practice & Research Clinical Gastroenterology.24(2010)299-310

Resection Procedure

- V-shape excision; Izbicki procedure
  - Non-dilated duct
  - Longitudinal V-shaped excision of the ventral aspect of the pancreas combined with a longitudinal pancreaticojejunostomy
  - In case of enlarged pancreatic head
    -> Pancreatic head resection
  - Pain relief in 89% of the patients
  - Mortality 0%, Morbidity 19.6%

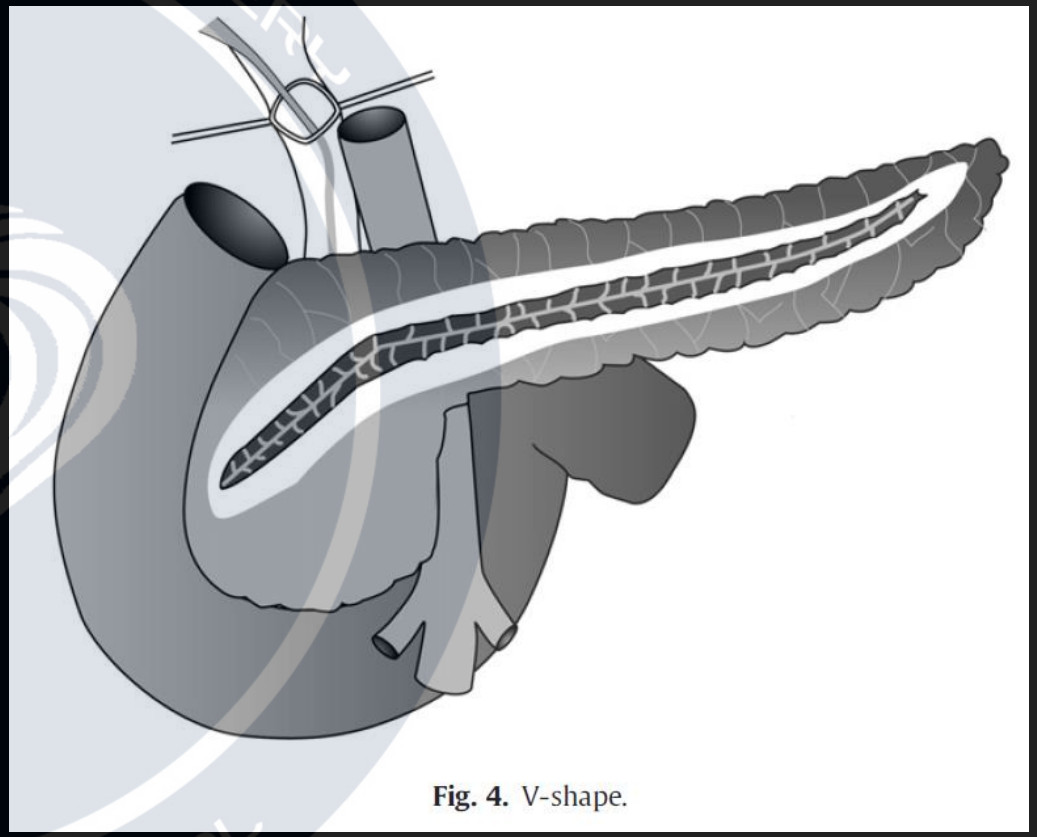


Fig. 4. V-shape.

K. Bachmannetal.Best Practice & Research Clinical Gastroenterology.24(2010)299-310

Resection Procedure

- Distal pancreatectomy
  - Only indicated if the inflammatory disease and complications resulting from inflammation in this region are localized on the left side of the gland
  - Resections of the distal part of the pancreas are often associated with endocrine insufficiency
  - Limited role in intractable pain management
  - High perioperative morbidity 30%

K. Bachmannetal.Best Practice & Research Clinical Gastroenterology 24(2010)299-310
J B Siegel et al. Journal of Surgical Research Volume 275, July 2022, Pages 29-34

Resection Procedure

- Total pancreatectomy with islet cells autotransplantation
  - Complete removal of the pancreas leads to complete relief of intractable pain in CP
  - Islet cell autotransplantation can avoid brittle DM in the respective patients
  - Considered in patients without duct system dilatation, who are resistant to conventional medical, endoscopic and previous surgical treatment and who have severe pain
  - Procedure of TPIAT
    - Total (potentially spleen preserving) pancreatectomy
    - Harvesting and purification of the islet cells
    - Reinfusion of the resulting suspension into the liver
      - Unselectively via the splenic vein stump
      - Selectively to the left liver lobe via a more centrally placed catheter in the left portal vein
  - Islet cells can take up function immediately after the operation
  - Overall improvement in quality of life in 90% of patients after 2 years and 85% after 5 years
    - Complete insulin independency is achieved in one third of patients
    - TPIAT can still lead to reduced dosages of insulin and improve glycemic control
  - End-stage disease with exocrine and complete endocrine failure are not suitable for it if there are few or no functioning islets present

BLUMGART'S Surgery *of the* Liver, Biliary Tract and Pancreas. 7th ed. 2023

Operation	Description	Indications
PD	Resection of the pancreatic head, duodenum, distal bile duct and antrum of the stomach	Focal disease at pancreatic head. Bile duct stricture, Duodenal stenosis, Suspicious pancreatic head mass
PPPD	Resection of the pancreatic head, duodenum and distal bile duct	Same as PD
DPPHR	Resection of the pancreatic head and distal bile duct. It has several variations including Beger, Frey, Berne and Hamburg	Pancreatic head mass with low suspicion of cancer
Beger Procedure	Resection of the pancreatic head at the portal vein, while sparing the duodenum with a rim of pancreatic tissue followed by a dual pancreaticojejunostomy. The bile duct is preserved	Same as DPPHR
Frey Procedure	Coring out of the pancreatic head away from the portal vein while preserving the duodenal blood supply and bile duct, followed by a lateral pancreaticojejunostomy	Same as DPPHR, Useful in the setting of portal hypertension with large collaterals
Berne modification	The pancreatic head is incised entirely leaving a rim of tissue on the portal vein. The exposed bile and pancreatic ducts are incorporated by an interposed jejunal loop	Same as DPPHR, Useful in the setting of portal hypertension with large collaterals
Hamburg modification	Wider resection of the pancreatic head and V-shaped incision of the anterior pancreas followed by a lateral pancreaticojejunostomy	Same as DPPHR, Useful in the setting of the non-dilated pancreatic duct
Izbicki procedure	Longitudinal V-shaped incision on the anterior surface of the pancreas incorporating secondary and tertriary order ducts followed by a lateral pancreaticojejunostomy	No pancreatic head mass with a non-dilated pancreatic duct
Puestow procedure	Transversely splitting the pancreas duct from tail to body just crossing the portal vein followed by lateral pancreaticojejunostomy, Classic Puestow procedure includes splenectomy	No pancreatic head mass with dilated pancreatic duct
Partington and Rochelle modification	The pancreatic duct is opened from the tail to just the right of the portal vein followed by a lateral pancreaticojejunostomy, The spleen and pancreatic tail are preserved	Same as the Puestow procedure
Total Pancreatectomy with islet autotransplantation	It requires the facility to isolate islet cells from the resected pancreas. The total volume required is 0.25 mL/kg with temporary occlusion of the portal vein if portal pressure crosses 25 cm H2O	Hereditary chronic pancreatitis with no risk of malignancy preferably in younger patients

Zafar H (March 06, 2023) Surgical Management of Chronic Pancreatitis: A Systemic Review. Cureus 15(3): e35806

Surgical Treatment

- Surgery is superior to endoscopy in terms of mid-term and long-term pain relief in patients with painful CP
  - Rarely first-line therapies and many surgeons only operate once endoscopic approaches to pancreatic drainage have been exhausted or unsuccessful
- Early surgery is favored over surgery at a more advanced stage of the disease
  - Achieve optimal long-term pain relief
  - Lower risk of developing PEI
    - Pancreatic resection techniques have a higher risk of PEI than drainage techniques
  - No recommendation of early surgery on endocrine pancreatic function
  - Improve long-term QoL

Lo¨hr et alUnited European Gastroenterology Journal 2017, Vol. 5(2) 153–199

Surgical Treatment

- Pancreatic exocrine insufficiency
  - Lower risk in early surgery than after surgery performed in an advanced disease stage
  - Pancreatic resection techniques have a higher risk for PEI than drainage techniques
- Endocrine pancreatic function
  - Few and contradicting studies on effect of early surgery
- Long-term quality of life is improved after early surgery (<3 years of onset) compared to surgery in a more advanced stage of disease

M.A. Kempeneers et al. . Pancreatology 20 (2020) 149-157

Surgical Treatment

- Timing for surgery
  - Suggest beneficial role for early surgery
    - Within the first 2-3 years after diagnosis or symptom onset
    - For patients who had equal to or fewer than 5 endoscopic procedures
    - For patients who have not yet required opioid analgesics for medical pain treatment

A.M. Drewes et al. Guidelines for the understanding and management of pain in chronic Pancreatitis. Pancreatology 17 (2017) 720-731

  - ASGE suggest surgical evaluation initiation of endoscopic management in patients with painful CP and an obstructed main PD
    - Contraindications to surgery or those who prefer a less-invasive modality-> endoscopic management as the initial approach

The ASGE Standards of Practice Committee. Gastrointestinal Endoscopy Volume 100, No. 4 : 2024

JAMA | Original Investigation

Effect of Early Surgery vs Endoscopy-First Approach on Pain in Patients With Chronic Pancreatitis
The ESCAPE Randomized Clinical Trial

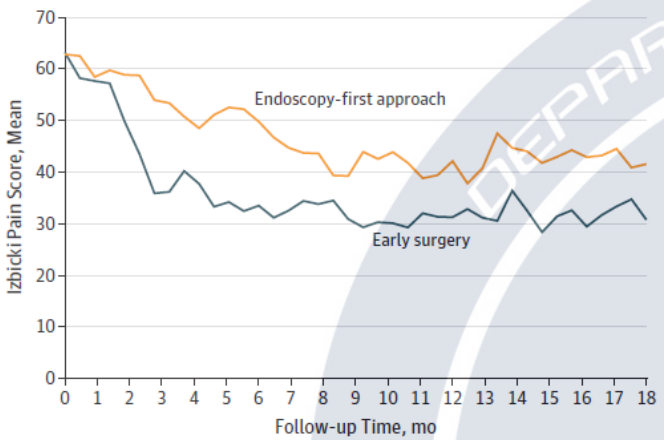
Yama Issa, MD, PhD; Marinus A. Kempeneers, BS; Marco J. Bruno, MD, PhD; Paul Fockens, M
Usama Ahmed Ali, MD, PhD; Thomas L. Bollen, MD, PhD; Olivier R. Busch, MD, PhD; Cees H
Peter van Duijvendijk, MD, PhD; Hendrik M. van Dullemen, MD, PhD; Casper H. van Eijck, M
Muhammed Hadithi, MD, PhD; Jan-Willem Haveman, MD, PhD; Yolande Keulemans, MD, Ph
Alexander C. Poen, MD, PhD; Erik A. Rauws, MD, PhD; Adriaan C. Tan, MD, PhD; Willem Thij
Ben J. Witteman, MD, PhD; Marc G. Besselink, MD, PhD; Jeanin E. van Hooft, MD, PhD, MBA
Marcel G. Dijkgraaf, PhD; Marja A. Boermeester, MD, PhD; for the Dutch Pancreatitis Study

- JAMA 2020
- Multicenter RCT comparing early surgery vs endoscopic first approach
- 88 patients, 44 in surgery group and 44 in endoscopy group
  - Sx group : Sx within 6 wk after randomization
  - Endoscopic first : Optimal medical Rx -> Endoscopy in failed medical Rx patients
- Primary outcome : pain, Secondary : pain relief at the end of follow up 18 mo
- Endoscopy group
  - Medical Rx fail : evaluate at 6 weeks
  - Endoscopic Rx fail : High pain score more than 6 wks despite 3 maximum endoscopic Rx or stent in need > 1 yr

Table 2. Primary and Secondary Outcomes

	Early Surgery (n = 44)[a]	Endoscopy-First Approach (n = 44)[a]	Early Surgery vs Endoscopy-First, Difference (95% CI)	*P* Value
Izbicki score: primary analysis[b]				
Area under curve	37 (25)	49 (25)	−12 (−22 to −2)	.02
Corrected area under curve[c]	34 (21)	52 (29)	−18 (−29 to −7)	.001
Izbicki score: per protocol[b]				
No. of patients	33	32		
Area under curve	33 (26)	46 (25)	−13 (−25 to −0.1)	.05
Corrected area under curve[c]	30 (21)	50 (30)	−20 (−33 to −7)	.003
Patients with some pain relief at end of follow-up, No./total No. (%)	23/40 (58)	16/41 (39)	19 (−4 to 41)	.10
Complete relief[d]	12/40 (35)	8/41 (20)		
Partial relief[d]	11/40 (23)	8/41 (20)		
Izbicki score at end of follow-up[b]	31 (29)	42 (32)	−11 (−25 to 3)	.13
VAS score during follow-up[e]	28 (22)	36 (17)	−9 (−17 to −1)	.03
Büchler pain score during follow-up[f]	36 (26)	51 (21)	−14 (−24 to −5)	.004
SF-36 quality of life during follow-up[g]				
Physical health scale	39 (12)	36 (9)	3 (−2 to 8)	.21
Mental health scale	44 (11)	41 (11)	3 (−2 to 8)	.21
Disease progression, No./total No. (%)				
Pseudocysts	2/44 (5)	6/44 (14)	−9 (−21 to 3)	.27
Chronic opioid use[h]	20/42 (47)	26/42 (60)	−14 (−35 to 7)	.20
Chronic pancreatitis flare-up	18/44 (41)	20/44 (46)	−5 (−26 to 17)	.67
Flare-ups per patient, median (IQR)	0 (0 to 1)	0 (0 to 1)	0 (0 to 0)	.52
Exocrine insufficiency, No./total No. (%)[i]	37/40 (93)	37/41 (90)	3 (−10 to 15)	>.99
Endocrine insufficiency, No. (%)[j]	12 (27)	19 (43)	−16 (−36 to 4)	.12
Hospital admissions, median No. per patient (IQR)	2 (1 to 2)	2 (1 to 4)	0 (−1 to 0)	.15
Hospital stay, median (IQR), d	11 (7 to 15)	10 (2 to 19)	1 (−3 to 5)	.57
Interventions per patient, median (IQR)	1 (1 to 1)	3 (2 to 4)	−2 (−3 to −1)	<.001
No. of endoscopic procedures ±ESWL[k]	0 (0 to 0)	3 (1 to 4)		
No. of surgical procedures	1 (1 to 1)	0 (0 to 1)		
Treatment complications, No. of patients (%)[l]	12 (27)	11 (25)	2 (−17 to 21)	.81

Figure 2. Mean Izbicki Pain Score During 18 Months of Follow-up



Early surgery																			
No. of patients	44	44	44	44	44	44	44	44	44	43	43	43	43	43	43	43	43	43	43
No. who underwent surgery (cumulative)	10	29	35	40	41	41	41	41	41	41	41	41	41	41	41	41	41	41	41
Endoscopy-first approach																			
No. of patients	44	44	44	43	43	43	43	43	43	43	43	43	43	43	42	42	42	42	42
No. who underwent surgery (cumulative)	0	0	0	0	0	1	2	6	6	7	7	7	7	9	10	12	12	12	13

Mean difference during follow-up for the early surgery group vs the endoscopy-first approach group: −12 (95% CI, −22 to −2); $P = .02$. The scale for the Izbicki pain score ranges from 0 to 100 points (increasing score indicates more pain severity). Questions consist of 4 items regarding frequency of pain, intensity of pain, use of pain medication, and disease-related inability to work (see eFigure 2 in Supplement 2 for scoring details).

- Endoscopy group : failed in 2/3 of patients
  - 13/44 patients of endoscopy group underwent surgery
  - Not all stenoses could be treated successfully, and strictures and stones often recurred
- Comparable complication
- Complete duct clearance in endoscopic group was comparable to surgical group

- Early surgery compared with an endoscopy-first approach resulted in lower pain scores when integrated over 18 months

JAMA Surgery | Original Investigation

Long-Term Outcomes of Early Surgery vs Endoscopy First in Chronic Pancreatitis

Follow-Up Analysis of the ESCAPE Randomized Clinical Trial

Charlotte L. van Veldhuisen, MD; Marinus A. Kempeneers, MD, PhD; Florence E. M. de Rijk, MD; Stefan A. Bouwense, MD, PhD; Marco J. Bruno, MD, PhD; Paul Fockens, MD, PhD; Jan W. Poley, MD, PhD; Usama Ahmed Ali, MD, PhD; Thomas L. Bollen, MD, PhD; Olivier R. Busch, MD, PhD; Peter van Duijvendijk, MD, PhD; Hendrik M. van Dullemen, MD; Casper H. van Eijck, MD, PhD; Harry Van Goor, MD, PhD; Muhanned Hadithi, MD; Jan-Willem Haveman, MD; Yolande Keulemans, MD; Vincent B. Nieuwenhuijs, MD; Alexander C. Poen, MD, PhD; Rogier P. Voermans, MD, PhD; Adriaan C. Tan, MD; Willem Thijs, MD; Robert C. Verdonk, , MD; Ben J. Witteman, MD; Jeanin E. van Hooft, MD, PhD; Hjalmar C. van Santvoort, MD, PhD; Marcel G. Dijkgraaf, MD, PhD; Marc G. Besselink, MD, PhD; Marja A. Boermeester, MD, PhD; Yama Issa, MD, PhD; for the Dutch Pancreatitis Study Group

- JAMA Nov 2024
- Compare long-term clinical outcomes of early surgery vs an endoscopy-first approach using follow-up data from the ESCAPE randomized clinical trial
- Approximately 8 yrs of follow-up
- Primary end point was pain, secondary end points included patient-reported complete pain relief and satisfaction

Table 1. Primary and Secondary End Points at Final Follow-Up

Outcome	Patients at end of long-term follow-up, No. (%)		
	Early surgery (n = 31)	Endoscopy-first approach (n = 30)	*P* value
Primary end point			
Izbicki pain score at end of follow up, mean (SD)	33 (31)	51 (31)	.03
Secondary end points			
Complete pain relief	14 (45)	6 (20)	.04
VAS score pain, mean (SD)	29 (29)	47 (31)	.02
SF-36 Quality of Life score, mean (SD)			
Physical health scale	45 (12)	42 (12)	.39
Mental health scale	42 (7)	42 (8)	.75
Pancreatic function			
Exocrine insufficiency[a]	25 (81)	26 (87)	.53
Endocrine insufficiency[b]	20 (64)	19 (63)	.92
Smoker			
Current	24 (77)	16 (53)	
Past	7 (23)	14 (47)	.05
Never	0	0	
Alcohol consumption			
Current	9 (29)	5 (17)	
Past	21 (68)	20 (67)	.15
Never	1 (3)	5 (17)	
Satisfaction result			
Very satisfied	22 (71)	10 (33)	
Partly satisfied	8 (26)	16 (53)	.003
Not satisfied	1 (3)[c]	4 (13)	
Would recommend treatment to family or friend	27 (87)	14 (47)	<.001

Abbreviations: SF-36, Medical Outcomes Study 36-Item Short-Form General Health Survey; VAS, visual analogue scale.

[a] Exocrine pancreatic function was assessed by the fecal elastase-1 function test, and a level less than 200 µg/g was defined as exocrine insufficient.

[b] Endocrine insufficiency was determined by the use of diabetes medication.

[c] Of all patients who underwent surgery.

- Pain score was lower in early surgery group
- Similar endocrine and exocrine function
- Additional interventions
  - 26% in surgery group (11 patients)
    - 9 : endoscopic Rx (CBD obstruction)
    - 2 : Sx
  - 44% in endoscopic group (19 patients)
    - 14 : Additional endoscopic Rx
    - 9 : Sx
- No differences between the early surgery and endoscopy-first for the formation of pseudocysts, chronic opioid use, flare-ups

eTable 6. Subgroup Analyses - Outcomes of Surgery in Early Surgery vs Surgery in Endoscopy-First[a]

Outcome	Surgical treatment outcomes at end of follow-up		
	Early Surgery (n=28)	Surgery in Endoscopy-First Approach (n=17)	p-value
Izbicki pain score at end of follow up	33 (31)	52 (24)	**0.027**
	Secondary endpoints - mean (SD)		
Complete pain relief, No. (%)	14 (55)	2 (12)	**0.019**
VAS score	29 (29)	50 (30)	**0.022**
SF-36 Quality of Life			
Physical health scale	45 (12)	43 (12)	0.632
Mental health scale	42 (7)	41 (8)	0.537

[a] Of the 61 patients who completed the end of follow-up survey with regards to pain and quality of life, a total of 46 patients underwent surgery during total follow-up. The effectiveness of surgery was evaluated and compared patients who received surgical treatment within the early surgery group and the surgery in the endoscopy-first group.

eTable 7. Subgroup Analyses - Endoscopy-First Approach (Duct Clearance Y/N)

Outcome	End of long-term follow-up		
	Endoscopy-first approach (N=28)		
	Endoscopic duct clearance (n=16)[a]	No endoscopic duct clearance (n=12)[a]	p-value
Izbicki pain score at end of follow up	45 (8) 49 (34)	54 (8) 53 (28)	0.688
Complete pain relief, No. (%)	4 (25)	2 (14)	0.475
VAS score	48 (34)	45 (29)	0.787
SF-36 Quality of Life			
Physical health scale	42 (10)	42 (13)	0.803
Mental health scale	43 (9)	40 (7)	0.330
Interventions per patient – median (IQR)	4 (4-6)	4 (2-5)	0.210
No. of endoscopic procedures	4 (3-5)	3 (1-4)	0.069
No. of surgical procedures	0 (0-1)	1 (0-1)	0.104

- Subgroup : Early Sx vs Sx in endo-first group
  - Pain score and complete pain relief were better in early Sx group, no difference in QoL
- Subgroup : Endoscopic ductal clearance
  - Mean pain score was not significant between complete or incomplete ductal clearance
- Subgroup : Pain score over time
  - Early Sx group : pain score was similar from 18 mo postop to long-term follow up
  - Endoscopy first : pain score worsened over time

eTable 9. Izbicki at Baseline, 18-Month Follow-Up and End of Long-Term Follow-Up, per Treatment Arm

Outcome	Izbicki pain scores, mean (SD)	
	Early surgery (n=27)	Endoscopy-first (n=23)
Mean Izbicki pain score (SD)		
Baseline	61 (20)*	63 (14)
18-month follow-up	29 (31)	39 (34)
End of long-term follow-up	32 (30)	49 (29)

Patients who completed baseline, 18-month follow-up and end of long-term follow-up Izbicki pain score survey were included in this analysis. Of the 61 patients who completed the end-of long-term follow-up survey, a total of 11 patients were therefore excluded from this analysis, leaving 27 patients in the early surgery group and 23 patients in the endoscopy-first group. At baseline, 4 patients did not fill out the baseline survey; 2 in early surgery and 2 in the endoscopy-first group. At 18-month follow-up, 7 patients did not fill out the 18-month follow-up survey; 2 in early surgery and 5 in the endoscopy-first group.

Surgical Treatment

- Chronic pancreatitis pain with enlarged pancreatic head
  - Diameter of >4 cm on CT or MRI imaging is usually considered as enlarged
  - Combined drainage and resection, such as Frey, Beger, and Berne procedure may be the treatment of choice
  - DPPHR vs conventional PD
    - Equally effective in relieving postoperative pain, comparable endocrine and exocrine insufficiency
    - Postoperative complication was superior in DPPHR compared to PD
    - QoL is significantly improved after DPPHR compared to PD
  - Neither DPPHR nor PD succeed in interrupting the progression of CP toward endocrine and exocrine failure

Lo¨hr et alUnited European Gastroenterology Journal 2017, Vol. 5(2) 153–199
M.A. Kempeneers et al. . Pancreatology 20 (2020) 149-157

Surgical Treatment

- Chronic pancreatitis pain with enlarged pancreatic head
  - Modifications of DPPHR – Beger and Berne procedures
    - Equal in terms of pain relief, postoperative morbidity and mortality
    - Operating time and length of hospital stay is significantly shorter for the Berne procedure than for the Beger
    - No differences of long-term outcome
  - Modifications of DPPHR – Beger and Frey
    - No difference in terms of pain relief, postoperative mortality and operating time
    - Intraoperative blood replacement and postoperative morbidity are significantly improved for the Frey procedure
  - The Frey and Berne procedures have similar results when compared to each other and to the Beger procedure from which they are both derived
    - The Frey and Berne procedures have however a lower morbidity rate with a comparable effect on pain control and quality of life

Lo¨hr et alUnited European Gastroenterology Journal 2017, Vol. 5(2) 153–199
M.A. Kempeneers et al. . Pancreatology 20 (2020) 149-157

Surgical Treatment

- Painful chronic pancreatitis with dilated(>5mm) and normal size pancreatic head
  - Main pancreatic duct diameter of 5mm in the pancreatic body seems amenable to ductal drainage for the majority of pancreatic surgeons
    - Threshold of 5mm is therefore proposed as the definition of a ‘dilated main duct’
  - Lateral pancreaticojejunostomy with a Roux-en-Y loop and Frey’s procedure provide comparable pain control
  - However, no recommendation can be made for the preferred surgical technique in these patients

Lo¨hr et alUnited European Gastroenterology Journal 2017, Vol. 5(2) 153–199

Preoperative parameters	Procedures
Pancreatic head mass with suspicion of malignancy	PD and PPPD [5]
Pancreatic head mass with dilated pancreatic duct	DPPHR Beger procedure [19]. Frey procedure [20]. Berne modification [21]
Pancreatic head mass with small pancreatic duct	Hamburg modification [21]
Dilated pancreatic duct with no head mass	Puestow procedure [23]. Partington and Rochelle modification [24]
Small pancreatic duct with no head mass	Izbicki procedure [22]
Hereditary pancreatic syndromes, diffuse pancreatic parenchymal disease, refractory disease in young	Total pancreatectomy with islet autotransplantation [26]

TABLE 4: Preoperative parameters and relevant procedures.

DPPHR: duodenum-preserving pancreatic head resection; PD: pancreaticoduodenectomy; PPPD: pylorus-preserving pancreaticoduodenectomy

Zafar H (March 06, 2023) Surgical Management of Chronic Pancreatitis: A Systemic Review. Cureus 15(3): e35806

Surgical Treatment

- Pain relapse after endoscopic or surgical management
  - Exclusion of obstructing stones or strictured anastomosis via imaging
  - Followed by a limited number endoscopic interventions, and early consideration of re-surgery to achieve pain control

A.M. Drewes et al. Pancreatology 17 (2017) 720-731

Mimic of Chronic Pancreatitis

Pancreatic Cancer

- Increased risk of PDAC in those with an underlying diagnosis of CP , cumulative risk of developing PDAC of 4.0%
  - Affected by multiple variables, including shared risk factors for cigarette smoking, alcohol use, and diabetes mellitus
  - Influenced by chronic inflammation and over-proliferation of pancreatic stellate cells
- 2 subtypes associated with markedly increased risk of PDAC : PRSS1 hereditary pancreatitis and Tropical pancreatitis, a form of calcific CP primarily described in Asia
- Mass forming pancreatic mass vs PDAC
  - 27%–50% of patients present with a localized mass or mass forming pancreatitis
    - 71% of focal lesions manifest in the pancreatic head

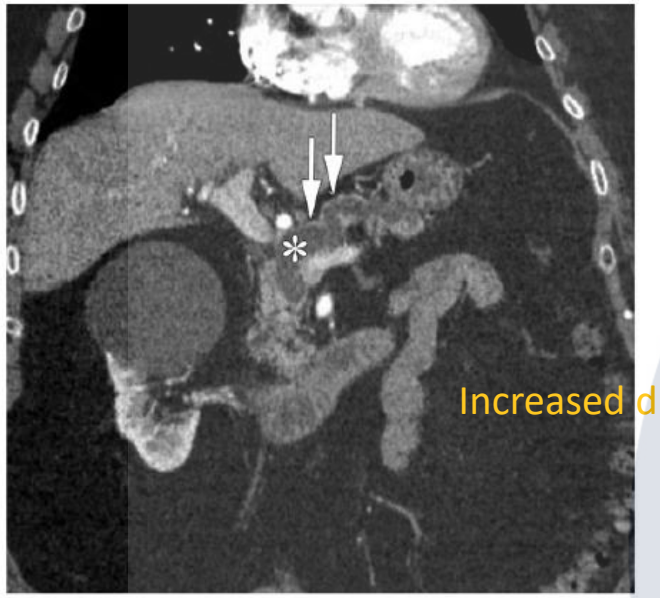
Ramsey et al. Dig Dis Sci. 2018; 63(7): 1745–1750
Wolske et al. RadioGraphics 2019; 39:1965–1982

Table 1: Summary of Imaging Findings of Mass-forming Pancreatitis and PDAC

Imaging Finding	Mass-forming Pancreatitis	PDAC	Comments
Duct-penetrating sign	May be present	Typically absent	Reliable sign of a benign abnormality (specificity, 96%; sensitivity, 85%), seen with mass-forming pancreatitis, AIP, and PDP
Collateral duct dilatation	May be present	Typically absent	Inflammation causes traction over the side branches and dilatation
Duct-to-parenchyma ratio >0.34	Typically absent	May be present	Smooth pancreatic ductal dilatation with an atrophic overlying parenchyma; reliable sign of malignancy (specificity, 97%; sensitivity, 94%)
Displaced calcifications	Typically absent	May be present	Mass evolving from preexisting chronic pancreatitis displaces the calcification toward the periphery
Double duct sign	Typically absent	May be present	Peripapillary obstruction (specificity, 63%–80%; sensitivity, 50%–76%)
SMA-to-SMV ratio >1	Typically absent	May be present	Peritumoral fatty infiltration may lead to deformity and decreased caliber of the SMV. Usually, the SMV is larger in diameter than the SMA. This sign, along with other supportive imaging signs, may help in making a diagnosis.
Vessel encasement or deformity	Typically absent	May be present	Occasionally, AIP can have perivascular inflammatory stranding mimicking PDAC

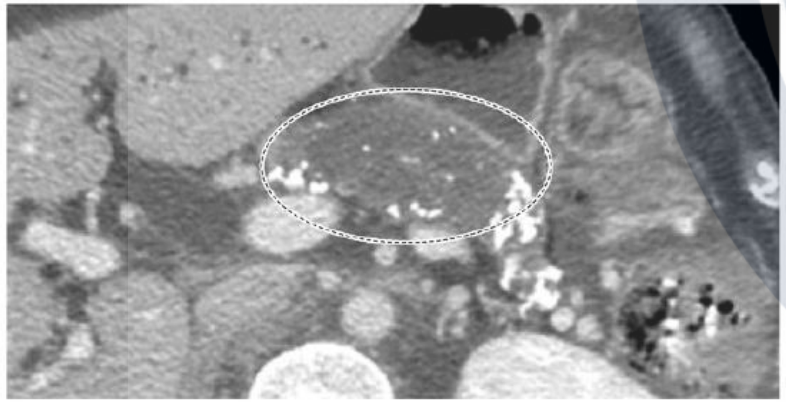
Note.—The online supplemental version of the table (Table E1) includes reference images.

Wolske et al. RadioGraphics 2019; 39:1965–1982

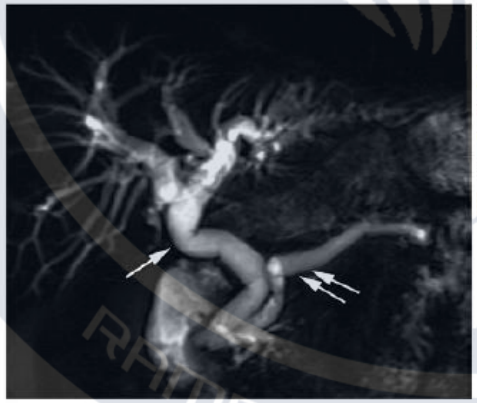


Increased duct-to-parenchyma ratio

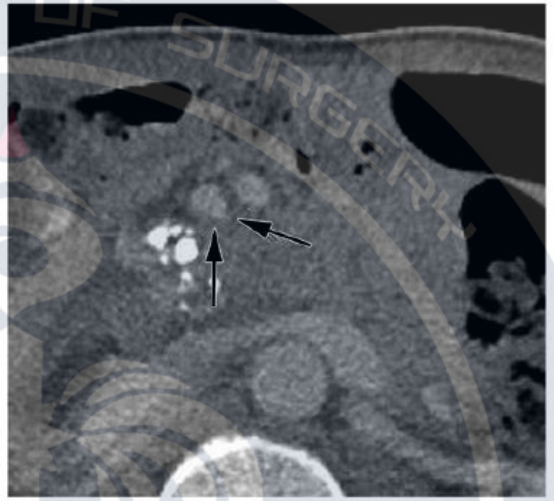
a.



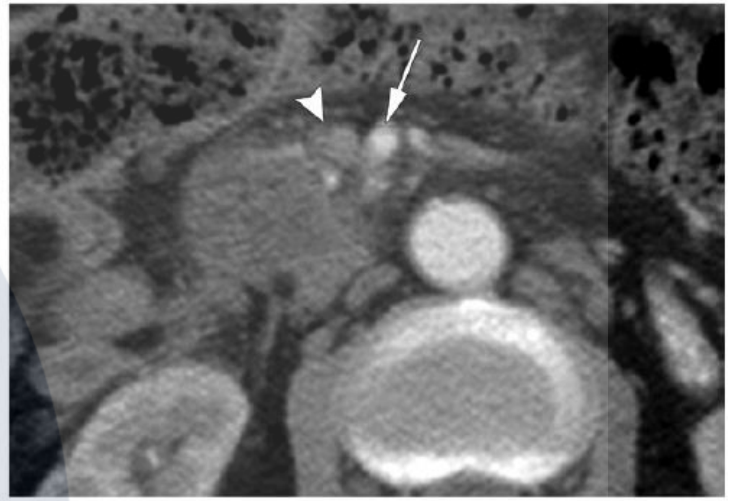
b. Displaced calcification



c. Double duct sign



d. Teardrop sign



e. SMA-SMV ratio

Figure 2. Imaging findings that favor diagnosis of a malignancy rather than an inflammatory condition. (a) Coronal CT image shows a duct-to-parenchyma ratio (maximum diameter of the diffusely dilated main pancreatic duct [*] and the overlying atrophic parenchyma [arrows]) of greater than 0.5). (b) Axial CT image shows diffuse calcifications in the background parenchyma and peripheral displacement of calcifications by a focal hypoattenuating lesion (dotted circle) in the pancreatic body. (c) MR cholangiopancreatogram shows the double duct sign, or dilatation of both the pancreatic duct (double arrows) and the common bile duct (single arrow). (d) Axial CT image shows the teardrop sign (arrows), a teardrop-shaped deformity of the SMV due to vascular encasement. Note the loss of fat in the perivascular space. (e) Axial CT image shows the SMA-to-SMV ratio, or the decreased caliber of the SMV (arrowhead) (almost the same size as the SMA [arrow]), of greater than or equal to 1.0. Note the loss of fat in the perivascular space.

Wolske et al. RadioGraphics 2019; 39:1965–1982

Mimic of Chronic Pancreatitis

Pancreatic Cancer

- Endoscopic ultrasound
  - Useful in distinguishing benign from malignant pancreatic mass lesions
  - Most studies show that EUS alone is not capable of precisely differentiating between a pseudotumoral mass and carcinoma in the setting of chronic pancreatitis
- Presence of multilobularity, homogenous pattern, hyperechoic septa and Doppler signal within a lesion favour pseudotumour

Dutta AK, Chacko A. Head mass in chronic pancreatitis: Inflammatory or malignant. *World J Gastrointest Endosc* 2015; 7(3): 258-264

Mimic of Chronic Pancreatitis

Pancreatic Cancer

- Endoscopic ultrasound c FNA
  - Can give the tissue diagnosis
  - FNA is relatively safe as it does not traverse peritoneal cavity and avoids seeding of peritoneum
    - Sensitivity of above 90% in detecting pancreatic malignancy in normal pancreas
    - Sensitivity dropping to below 75% in chronic pancreatitis
  - Microsatellite marker and k-ras mutation testing on FNA specimen can increase sensitivity

Table 1 Endoscopic ultrasound in evaluating pancreatic mass lesions in patients with chronic pancreatitis

Ref.	Study subjects	Procedure	Outcome[1]
Fritscher-Ravens *et al*[19]	74 patients with focal pancreatic lesions and chronic pancreatitis	EUS FNA	Sn-54%
Vardarajulu *et al*[17]	75 patients with CP and focal pancreatic mass lesion	EUS FNA	Sn-73.9% Sp-100%
Iordache *et al*[18]	CP-55 CP and PC-17	EUS FNA	Sn-50% Sp-73.7%
Hocke *et al*[13]	86 patients with CP and pancreatic lesion	EUS	Sn-73.2% Sp-83.3%
		CE-EUS	Sn-91.1% Sp-93.3%

[1]Differentiating malignant and non-malignant pancreatic lesion. Sn: Sensitivity; Sp: Specificity; CP: Chronic pancreatitis; PC: Pancreatic cancer; CE: Contrast enhanced; EUS: Endoscopic ultrasound; FNA: Fine needle aspiration.

Dutta AK, Chacko A. Head mass in chronic pancreatitis: Inflammatory or malignant. *World J Gastrointest Endosc* 2015; 7(3): 258-264

Mimic of Chronic Pancreatitis

Pancreatic cancer

- Contrast-enhanced EUS
  - Useful in patients with renal failure
    - Microbubble contrast agents are not nephrotoxic
  - Detect the enhancement and washout of the lesion for evaluation of pancreatic mass
- Elastography
  - Noninvasive ultrasound technique which helps to assess the stiffness of a tissue
    - Fibrosis and malignant infiltration can increase the stiffness of tissue

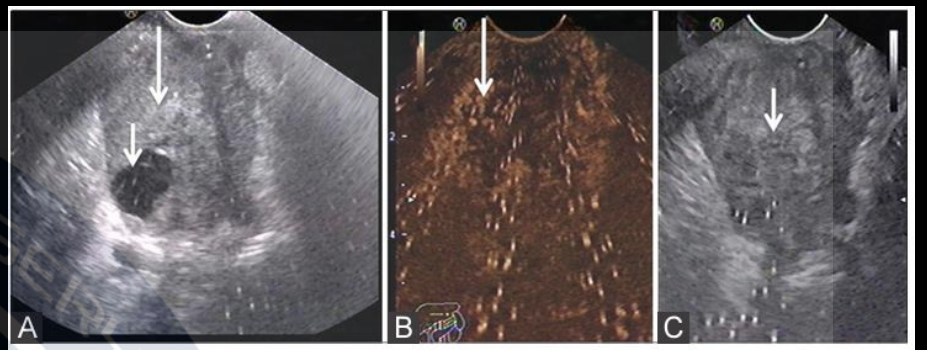


Figure 4 (A-C): Contrast-EUS in a patient with mass forming chronic pancreatitis shows a mass in the head of pancreas with cystic component (arrow, A) with peripheral enhancement (arrow, B) and central nonenhancing component. The central nonenhancing component is slightly echogenic than the rest of the mass (arrow, C). In long standing cases of mass forming chronic pancreatitis, this lack of enhancement mimics pancreatic adenocarcinoma

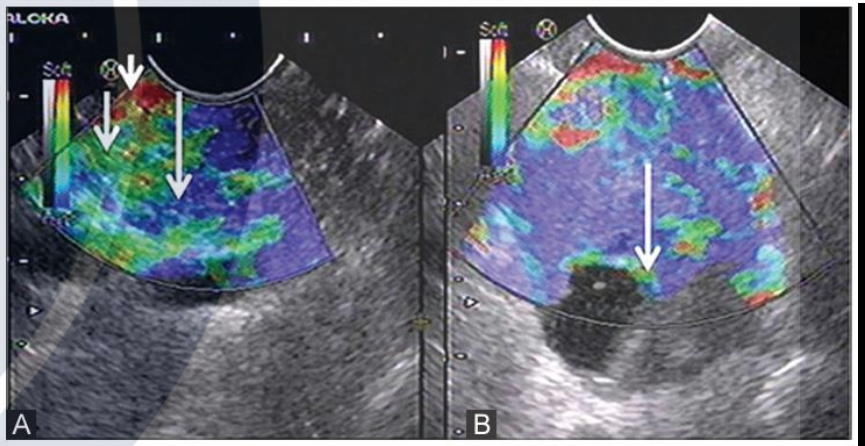


Figure 5 (A and B): EUS elastography in a patient with chronic pancreatitis shows heterogenous stiffness of the pancreas (A) with hard areas (arrow) and areas of intermediate stiffness (short arrow). In another patient with mass forming chronic pancreatitis (B), elastography shows that the mass is hard (blue areas). Also note the presence of a cyst (arrow)

Kamat, et al.: Imaging in chronic pancreatitis. Indian Journal of Radiology and Imaging / Volume 29 / Issue 2 / April-June 2019

Mimic of Chronic Pancreatitis

Pancreatic cancer

- FDG PET
  - The standardized uptake value (SUV) of FDG is significantly greater in malignant masses of the pancreas compared with focal pancreatic masses in CP
    - SUV >4 is usually seen in a pancreatic carcinoma
    - SUV of 3-4 is more commonly seen in cases of focal pancreatic masses in CP
    - SUV <3 is seen in healthy individuals
  - Sensitivity and specificity are between 81 and 100% and 65 and 100%, respectively, for diagnosing carcinoma in cases of focal pancreatic masses

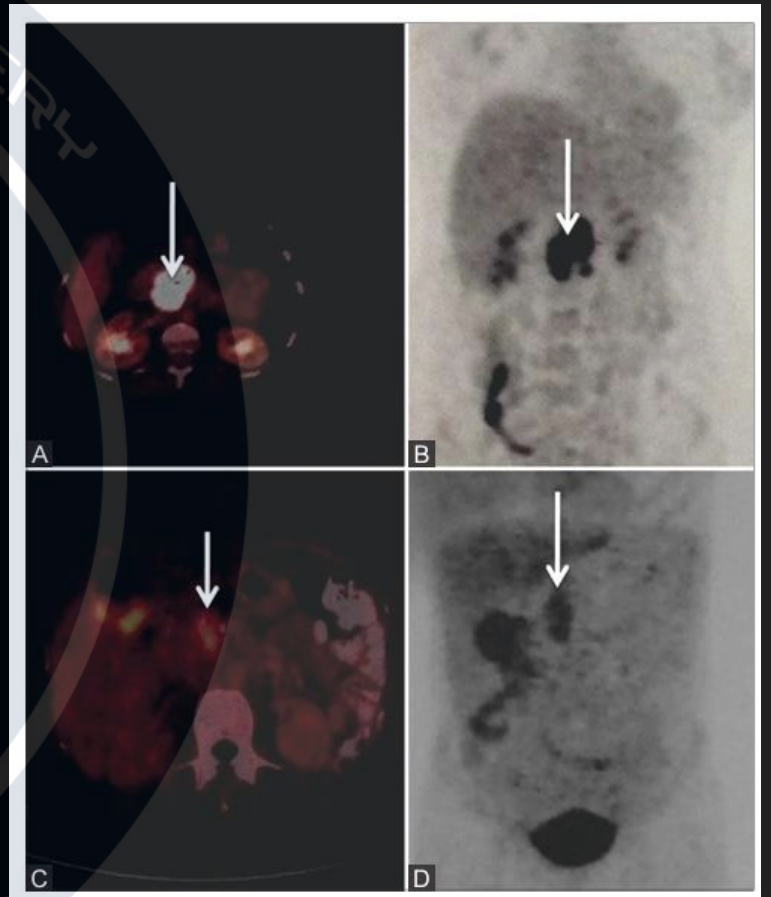


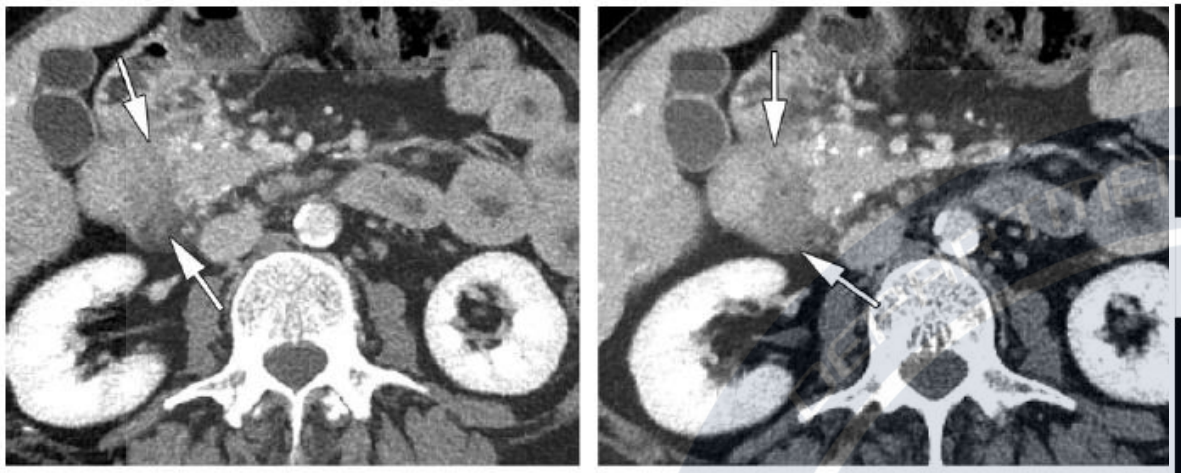
Figure 11 (A-D): FDG-PET in chronic pancreatitis: Axial PET image (A) and corresponding coronal MIP image (B) shows marked FDG avidity (SUV max-12) in the pancreatic head mass in a patient with pancreatic adenocarcinoma. In a patient with mass forming chronic pancreatitis show PET shows low FDG avidity in the pancreatic head mass (arrow, C and D)

Kamat, et al.: Imaging in chronic pancreatitis. Indian Journal of Radiology and Imaging / Volume 29 / Issue 2 / April-June 2019

Mimic of Chronic Pancreatitis

- Paraduodenal pancreatitis; Groove pancreatitis
  - Focal form of pancreatitis centered at the pancreaticoduodenal groove
    - Inflammation and fibrosis can form pseudotumor-> mimicking locally invasive PDAC
  - 3 distinct subtypes
    - The solid tumoral type (type 1), manifests as a solid pseudotumor with minimal cystic change
      - Solid appearing sheet-like mass at pancreaticoduodenal groove -> Difficult to distinguish from PDAC
    - The cyst-forming type (type 2 PDP), lesions are predominantly cystic, with cysts accounting for greater than 80% of the lesion
    - The ill-defined type (type 3), is not like a mass and is, therefore, less likely to mimic malignancy

Wolske et al. RadioGraphics 2019; 39:1965–1982



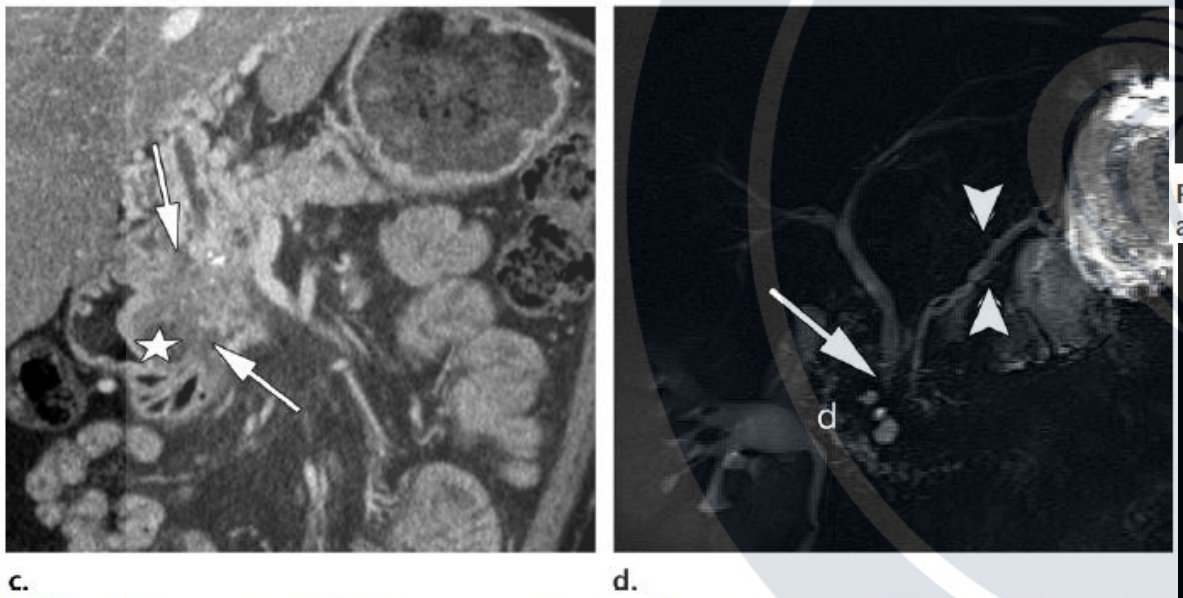


Figure 11. Type 1 solid PDP (groove pancreatitis) in a 39-year-old man. (**a**, **b**) Axial CT images show an ill-defined hypoattenuating masslike lesion in the duodenopancreatic groove (arrows). Scattered parenchymal calcifications appear in the pancreatic head. (**c**) Coronal CT image shows the extent of the masslike lesion in the duodenopancreatic groove (arrows) and associated cystic changes in the duodenal wall (☆). The distal common bile duct is partially visible. (**d**) MR cholangiopancreatogram shows focal narrowing of the distal common bile duct (arrow) and subtle prominence of the side branches (arrowheads). Note the widening of the duodenopancreatic groove and cystic changes in the duodenal wall *(d)*.

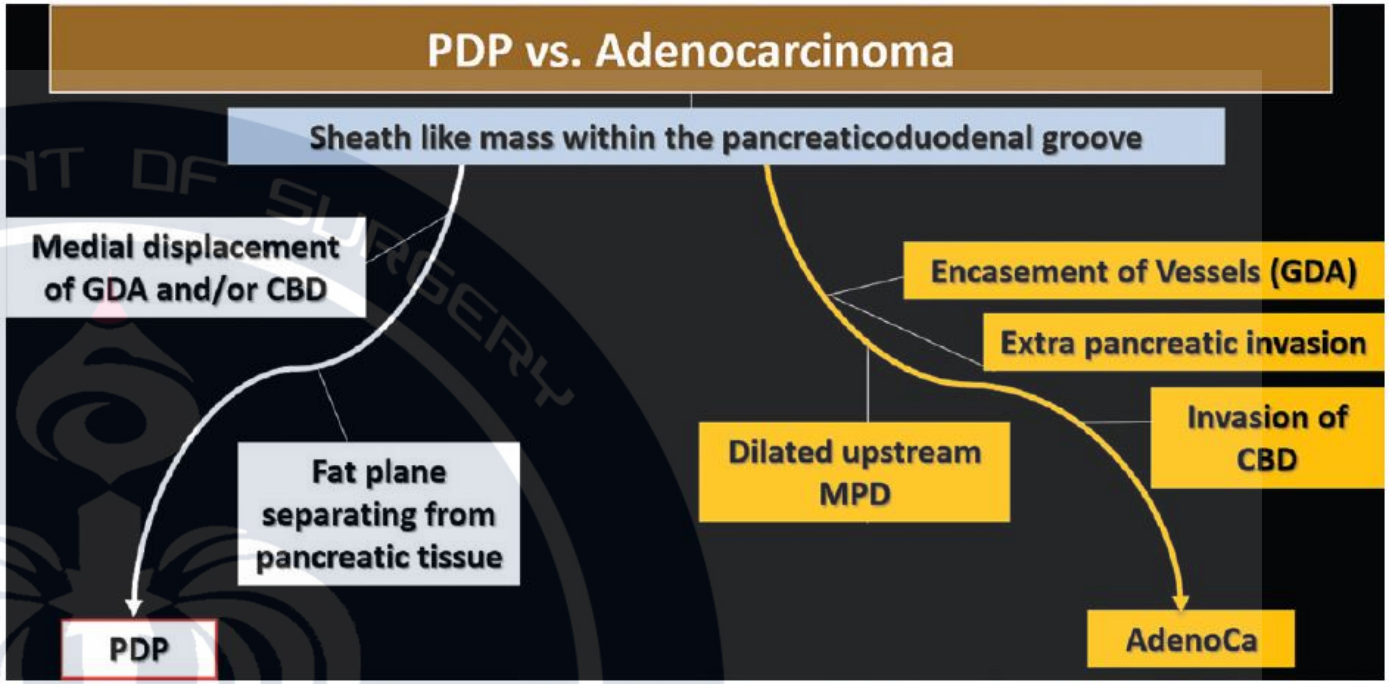


Figure 13. Diagnostic approach in a case of suspected solid variant PDP (groove pancreatitis) or PDAC. *AdenoCa* = adenocarcinoma, *CBD* = common bile duct, *GDA* = gastroduodenal artery, *MDP* = main pancreatic duct.

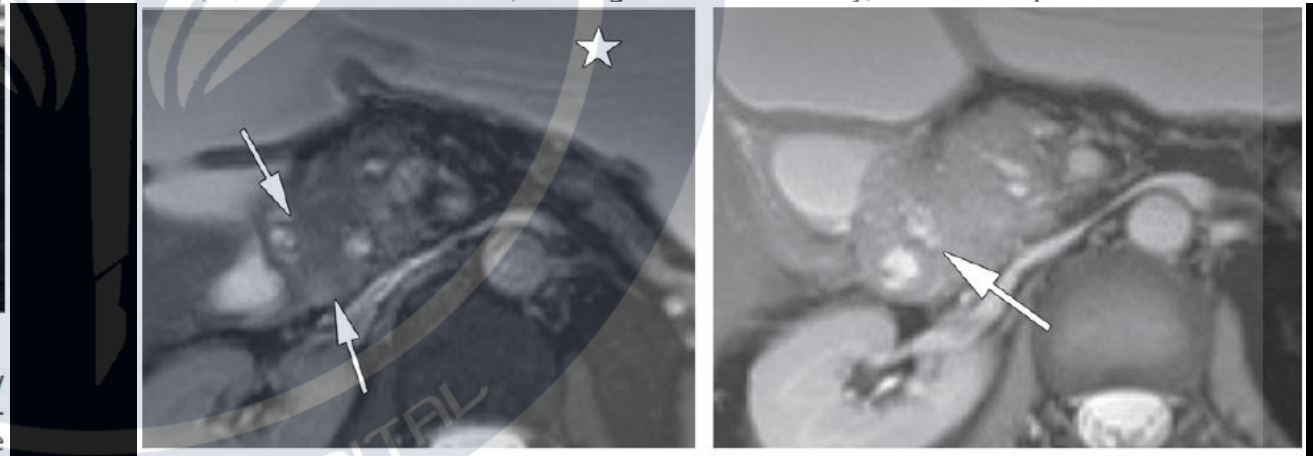


Figure 12. Type 1 solid PDP (groove pancreatitis) in a 41-year-old man. (**a**) Axial fat-suppressed T2-weighted MR image shows an ill-defined masslike thickening of the medial duodenal wall, with intermediate signal intensity (arrows). At presentation, the patient was found to have duodenal outlet obstruction. Note the dilated stomach (☆). (**b**) Axial fat-suppressed T2-weighted MR image shows a predominantly solid masslike area in the pancreatic head and microcystic changes along the duodenal wall (arrow).

Chronic Pancreatitis: Sukhum Kobdej,MD.(F)

Wolske et al. RadioGraphics 2019; 39:1965–1982

Mimic of Chronic Pancreatitis

- The initial treatment of groove pancreatitis should involve medical treatment and occasionally, endoscopic drainage procedures may be helpful
  - Surgery in these failed approaches fail
- In expert hands, pancreaticoduodenectomy is the most suitable surgical option for patients with groove pancreatitis

Lo¨hr et alUnited European Gastroenterology Journal 2017, Vol. 5(2) 153–199

Mimic of Chronic Pancreatitis

- Obstructive chronic pancreatitis
  - Subtype of chronic pancreatitis where the duct demonstrates a uniform contour and diffusely dilated appearance
    - Periductal fibrosis and subsequent ductal dilatation
    - Diffuse ductal changes : secondary to chronic inflammatory stenosis of the papilla after repeated microtrauma -> Leads to fibrosis and narrowing of the sphincter of Oddi
  - Obstruction and diffused duct dilatation -> DDx juxtapapillary neoplasm, Main duct IPMN

Wolske et al. RadioGraphics 2019; 39:1965–1982

Table 3: Differentiating among OCP, IPMN, and Juxtapapillary Neoplasms at Imaging

Imaging Features	OCP	IPMN	Juxtapapillary Neoplasms
Gland atrophy	Present or absent	Present/absent	Strongly present
Parenchymal calcification	Strongly present	Present/absent	Present or absent
Solid enhancing mass	Absent	Absent	Present
Double duct sign	Present or absent	Absent	Strongly present
Protrusion of major papilla into duodenum	Absent	Strongly present	Present or absent, with enhancing mass
Nodular enhancement along the wall of the pancreatic duct	Absent	Strongly present	Absent
Cystic ectasia of the branch ducts	Absent	Strongly present	Absent
Mucinous deposits within the ductal lumen	Absent	Strongly present	Absent

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Complication of Chronic Pancreatitis

Pseudocysts

- Prevalence 20-40 %
- Symptoms associated with a pseudocyst depends on the cyst size and anatomic location
  - Abdominal pain, early satiety, nausea/vomiting, jaundice, and weight loss
- Spontaneous resolution in less than 10% in chronic pancreatitis
- Secondary complications that may occur due to pseudocysts include duodenal and/or biliary obstruction, SVT, and rarely infection
- Management
  - Endoscopic treatment : Endoscopic cystogastrostomy has been borrowed from the management of walled off necrosis, to address symptomatic pancreatic pseudocysts
  - Surgical treatment : Intervention primarily involving either surgical resection (e.g., distal pancreatectomy) or surgical cystogastrostomy

Ramsey et al. Dig Dis Sci. 2017 July ; 62(7): 1745–1750

Complication of Chronic Pancreatitis

Duodenal obstruction

- Incidence approximately 1%; obstruction may be transient or fixed
  - Transient swelling occurs in the setting of an acute pancreatitis flare
  - Fixed obstructions occur secondary to compression from a peripancreatic fluid collection (pseudocysts) or fibrotic changes in the head of the pancreas
  - Groove pancreatitis -> Frequently complicated by duodenal obstruction
- Evaluation typically consists of both direct endoscopic visualization and cross-sectional imaging
- Patients with compression from a pancreatic pseudocyst can often be managed with endoscopic therapy
- Management of duodenal obstruction from CP due to fibrotic changes is primarily surgical
  - Palliative gastrojejunostomy, duodenum-preserving pancreatic head resection, or pancreaticoduodenectomy

Ramsey et al. Dig Dis Sci. 2017 July ; 62(7): 1745–1750

Complication of Chronic Pancreatitis

Pseudoaneurysm

- Erosion of pancreatic or nearby vessels by leaked pancreatic juice -> Permanent communication of invaded vessels to the CP-induced pseudocyst -> Pancreatic pseudoaneurysm
- Investigation
  - CT : first choice of diagnostic tool for CP complicated with a pseudoaneurysm, as it can delineate the anatomy and location of the bleeding pseudoaneurysm in detail
- Management
  - Angioembolization – first-line therapy to locate the bleeding site and stop the bleeding to stabilize vital signs
  - Surgical treatment – in fail arterial embolization for pseudoaneurysm bleeding
    - Located over the tail of the pancreas, resection is the preferred procedure(distal pancreatectomy)
    - Head or body of the pancreas, relatively conservative surgical procedures are recommended

Chiagn et al. World J Gastroenterol 2014 November 21; 20(43): 16132-16137

Complication of Chronic Pancreatitis

Splenic vein thrombosis

- Occur in both acute and chronic pancreatitis
- Develops in approximately 10-20% of CP
- Mostly asymptomatic
  - Some patients develop gastric varices -> GI bleeding
  - Splenomegaly
- Management is mostly conservative with monitoring for signs of bleeding from gastric varices
- Anticoagulation does not increase the odds of recanalization of the splenic vein in the setting of acute pancreatitis in one study
  - No data for CP-associated SVT

Ramsey et al. Dig Dis Sci. 2017 July ; 62(7): 1745–1750

Thank You